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Archives of Neurology and Psychiatry

VOLUME 25 FEBRUARY, 1931 NUMBER 2

ACUTE DISEASES OF THE BRAIN DUE TO FUNCTIONAL DISTURBANCE OF THE CIRCULATION

LAMINATED CORTICAL DISEASE *

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In this article I shall deal with some acute cases of cerebral disease in which multiple lesions of vascular origin, electively localized in the cortical gray matter, form the most interesting part of, or even the entire, pathologic process. The etiology varies; in two cases toxemia of pregnancy was the probable cause; in one case encephalitis and in one case severe shock with fall of the blood pressure. One patient died in the acute stage; the others survived from four to eight weeks.

There is still considerable confusion in the literature about the rôle played by primary blood vessel disease in cerebral lesions, evidenced, for instance, by the tenacity with which the term encephalitis hemorrhagica is being used for conditions in which no inflammation is present (case 1). On the other hand, it is difficult to recognize during life which part of the symptoms in a case of brain disease is due to the direct action of the disease on the nerve tissues, and which part to its action on the blood vessels of this organ (case 3, in which encephalitis was accompanied by extensive brain destruction of vascular origin).

REPORT OF CASES

CASE 1.—*Acute eclampsia; cerebral purpura and multiple small foci of softening in the cortex.*

Clinical History.—A Chinese woman, aged 42, began labor with pain in the eighth month of pregnancy. Shortly afterward, she had an attack of eclampsia and remained unconscious until death. When she was admitted to the hospital, shortly after the first convulsion, it was found that she was icteric, but it was impossible to ascertain when icterus had developed. The patient had several eclamptic convulsions, and died on the day after admission, fifty hours after the first symptoms of eclampsia (headache). The past history was without signifiance. The patient had not had any other serious diseases; the Wassermann reaction of the blood was negative. She had had headache for one day before the convulsions started; no edema, dizziness or blurring of vision were noted.

Examination.—On admission, marked jaundice was found, and there were petechial hemorrhages in the skin of the trunk and extremities, varying from pinpoint to 2 mm. in size. The breath smelled of acetone. The temperature was

* Submitted for publication, Feb. 10. 1930.

* From the Division of Neurology of the Peiping Union Medical College, Peiping, China, and the Central Dutch Institute for Brain Research, Amsterdam.

37.8 C. (100 F.). The blood pressure was 90 systolic and 70 diastolic (the patient was unconscious) and the pulse rate 110. The urine contained albumin. Examination of the blood showed 3,140,000 red cells, 24,300 white cells, with 87 per cent polymorphonuclears; nonprotein nitrogen 84.8, and carbon dioxide-combining power 10.7 per cent. An examination of the eyegrounds showed typical eclamptic fundus, with blurring along the vessels, but without hemorrhages. A dead baby was delivered spontaneously.

Autopsy.—There were: hemorrhages and necrosis of the liver, with jaundice; hemorrhages in the myocardium, urinary bladder, kidney pelves, suprarenal glands, skin and subcutaneous tissue; nephrosis; fatty change of the myocardium; subacute pericarditis and myocarditis, and hyaline change of the wall of the splenic arteries.

The brain was not swollen, but the meninges and cortex were anemic. No hemorrhages were found in the meninges. The large vessels are not sclerotic; the ventricles were not enlarged. On cutting the brain, it was noted that everywhere in the cortex there were hemorrhagic spots, mostly punctiform, but sometimes larger or grouped together in patches of from 0.5 to 1 cm. They were found only in the cerebral cortex; none could be seen in the white matter, basal ganglia, pons, cerebellum or other structures. The distribution in the cortex was diffuse; both hemispheres contained them in nearly symmetrical distribution. They lay in the areas of all three main arteries, perhaps in larger number in the frontoparietal region. In places where hemorrhages were grouped together, the consistency of the tissue was softer than normal.

Microscopic Examination.—The outstanding fact was that the hemorrhages were secondary in importance to small foci of softening, of which they were probably the consequence and not the cause. Figure 1 gives a good idea of the distribution of the foci in the cortex. As is easily seen, the areas of softening occupied various layers of the cortex, and in no instance was the cortex changed in its entire depth. Most of the foci stopped abruptly before the white matter was reached, but sometimes the latter was involved to a small extent. No foci were found in the white matter only.

In a focus one often found a small artery with a degenerated wall, which was sometimes vacuolated and filled with fat (fig. 2). The endothelial cells were well preserved in many of these vessels, but seemed to be necrotic in other parts. Often these arteries were filled with hyaline thrombi (fig. 3), but the artery leading to a focus and the pial vessels were never thrombosed. In the foci most of the ganglion cells had disappeared, and the remaining cells were invariably pyknotic and shrunken. There was no total softening of the tissue; the molecular substance was still present, although it did not stain as readily with van Gieson or eosin stains as usual. Most of the glia cells had also disappeared, and there was no proliferative vascular or glial reaction. In some places, however, red blood corpuscles lay in the perivascular spaces, or, especially in the periphery of the foci, also in the nerve tissue. This was probably diapedesis from adjacent vessels. Here also one could observe sometimes a beginning exudation of polymorphonuclear leukocytes.

The adjoining parts of the cortex were not quite normal: many ganglion cells were swollen and vacuolated; others showed other forms of acute degeneration, with little or no signs of neuronophagia. The ganglion cells in other parts of the cortex not near necrotic foci were much better preserved. The glia of the superficial layer was necrotic in the parts that were seriously affected, but showed proliferation in the areas near the normal cortex. The pia was infiltrated with large macrophages; there was some transportation of débris in the pia, and lipo-

fuscin pigment, absorbed by phagocytes, was found everywhere in the pia. This was also found along the vessels of the white matter. The blood vessels in other parts of the cortex were normal or showed a small degree of thickening of their wall, without necrosis.

In other parts of the brain, microscopic examination showed fatty degeneration of ganglion cells of the cortex and also degeneration of the Purkinje cells of the cerebellum. Mild sclerosis of the arteries could be observed in many places. The sylvian artery showed a marked endarteritis obliterans, without, however, considerable narrowing of its lumen.

Comment.—Labor started in the eighth month of pregnancy. The patient had several attacks of eclampsia, and showed icterus and petechial

Fig. 1 (case 1).—Eclampsia. General view of foci in the cortex. Note that the white matter is not affected; *f*, fissure; *c*, cortex; *w*, white matter. Paraffin, phosphotungstic hematoxylin.

hemorrhages of the skin. She remained unconscious and died fifty hours after the headache started, thirty hours after the first eclamptic attack. The changes in the brain were primarily vascular. The foci of softening were due to arterial occlusion, and the hemorrhages were probably the result of necrosis of the vessel walls and surrounding tissue. Thrombosis in the blood vessels was found in the foci of necrosis, but no changes in the arteries leading there could be made out, which seemed to exclude an organic obstruction as the cause, and pointed to a temporary occlusion.

The nearly total disappearance of the ganglion cells in the foci in thirty hours, the time between the first eclamptic attack and death, has also been described by various authors. The occurrence of lipofuscin in the pia and in the white matter was, however, a sign of chronic destruction of nerve tissue. The hemorrhage was of the type of diapedesis caused by stasis; typical rhexis hemorrhage was not found. Nor did I find typical ring hemorrhages with a vessel in a necrotic center. The larger foci, however, can be explained as large ring hemorrhages, in which the red blood cells do not form a closed ring, but lie irregularly arranged in the periphery of the necrotic focus. The condition of the

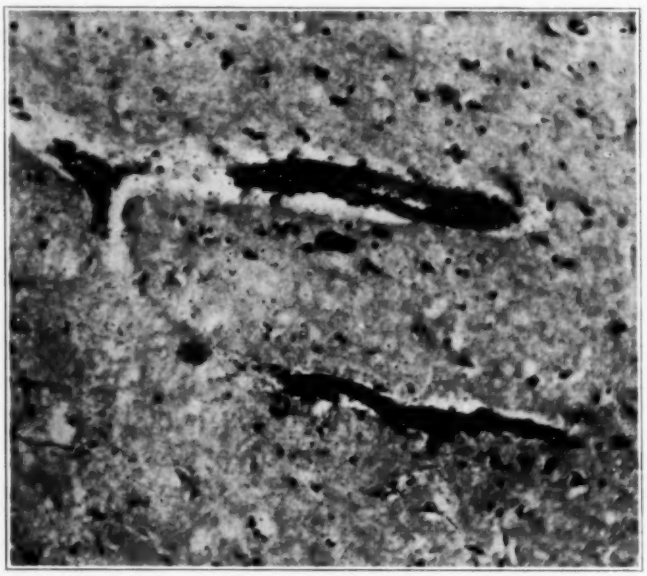

Fig. 2 (case 1).—Eclampsia. Fatty degeneration of the blood vessel walls. Note the dark small fat-droplets in the vessel wall. Frozen sections; scharlach R stain.

red blood cells in the hemorrhages varied; changes in their shape and color had already occurred in some, whereas others were fresh. There was not much evidence of general toxic action on the ganglion cells, although some degenerative changes were present everywhere. On the other hand, there was evidence of an older vascular lesion. The middle cerebral artery had a very thick wall in some places, due to chronic endarteritis (without evidence of mesarteritis). The smaller cortical arteries also showed thickening of their walls.

Case 2.—*Eclampsia (or uremia?) in the fifth month of pregnancy. Multiple laminated softening in the cortex.*

Clinical History.—A Chinese woman, aged 34, who had been pregnant since June, 1927, contracted relapsing fever in July, which was cured with one injection of arsphenamine. In August, she had an attack of diarrhea. She was normal after that until the middle of October, when she noticed some edema of the legs. On October 31, she complained of severe headache and some blurring of vision. On the next day she had nausea and vomited, and early in the morning started to have generalized convulsions. She had six or seven convulsions at intervals of about ten minutes. After that, consciousness was clouded; at times she did recognize her surroundings; at other times she was unconscious. On the next day, she had six more attacks.

Examination.—On November 3, on her admission to the hospital, the temperature was normal and the pulse rate 120. She was conscious and answered

Fig. 3 (case 1).—Eclampsia. Foci of necrosis with thrombosis of arteries. Note that the feeding artery in the cortex and the arteries in the pia are normal. Celloidin, van Gieson stain.

questions. No convulsions were seen after admission. The blood pressure was 195 systolic and 110 diastolic. The blood contained 54.5 mg. of nonprotein nitrogen per hundred cubic centimeters and 6.6 mg. of creatinine, values that are above the normal upper limit. The urine contained albumin, and granular and hyaline casts. The white blood count was 15,100. The muscles were rigid, but no rigidity of the neck was found.

Neurologic Examination: The pupils were very small, but reacted to light; all tendon reflexes were absent; the plantar reflex was of extensor type on both sides. According to the nurse, the patient was able to move all four limbs, but no movements were observed during my examination.

The fetal heart sounds were heard on admission.

Course.—On November 4, hysterotomy was performed by the abdominal route, and a dead fetus was delivered. No complications followed immediately after the operation.

The temperature, which had already gone up before the operation, rose still higher, showing a continuous fever until the patient died four weeks later.

On November 7, the first signs of changes in the heart were noted. The patient was semicomatose; paralysis of both legs and of the right arm was also noted for the first time. On the next day, the coma was deeper; a Babinski sign was present on both sides; the left arm still could be moved; the eyeballs deviated to the right. The spinal fluid pressure was 200 mm.; the fluid was clear and colorless, and showed a normal protein count and a few red blood cells. An examination of the eyegrounds revealed papilledema in both eyes.

After the operation there was a rapid decrease in the red blood cells; they numbered 5,350,000 on admission, 3,600,000 on November 8, and 1,088,000 on November 21, when transfusion was done. Fever continued, and the general condition became progressively worse. Signs of nephritis were less than on admission. Consciousness was partly restored, but the patient remained unable to move both legs and the right hand. The blood pressure came down in a few days from the initial high pressure, but varied between 110 and 140 systolic pressure until five days before death, when it dropped to from 92 to 110 systolic and from 56 to 70 diastolic. A streptococcic infection of the vulva finally developed, which spread to a cellulitis of the left thigh; probably this was the direct cause of death on November 28. Blood cultures had been made repeatedly during the course of the disease, but had always been negative. Blood taken by heart puncture after death showed a hemolytic streptococcus.

Autopsy.—This was performed a few hours after death. There were: chronic and subacute diffuse nephritis; *Staphylococcus aureus* infection of surgical wounds in the uterus and abdominal wall; subacute endometritis, with generalized fibrinopurulent peritonitis; *Streptococcus haemolyticus* infection of the subcutaneous tissues of the left leg, with thrombosis of the femoral and pelvic veins. The changes in the kidneys were widespread, but focal, and varied widely in age.

On macroscopic examination, the brain did not show swelling or edema. The meninges were thin and transparent, but contained on the convex side of the left hemisphere some thrombosed veins. Injection of the capillaries was found around this place. There was no thrombosis of the smaller veins or of the longitudinal sinus. No hemorrhages were seen on the surface; no softened areas were found. There was no sclerosis of the basal arteries and no thrombosis or embolus in these or in their branches. After the brain was cut, however, numerous foci of softening were found in various places, in some of which there were punctate hemorrhages. Larger areas of softening were found in the central convolutions of both sides, and in both occipital lobes. The destruction of these larger foci, however, was limited to the cortex, leaving the white matter free. Long stretches of cortex were totally destroyed in this way. In addition to these larger foci, there were many small foci of softening; one in the white matter of the occipital lobe, resembling (only macroscopically) a focus of multiple sclerosis; others in the right superior frontal convolution, in the point of the right temporal lobe, in the right caudate nucleus and in the left thalamus. The internal capsule was free, as were the cerebellum, mesencephalon, pons, medulla oblongata and spinal cord.

Microscopic Examination.—A section through the occipital lobe (fig. 4) showed that the greater part of the cortex was destroyed, and that all the myelinated fibers had disappeared. In only two places was normal cortex still found (fig. 4, *a*).

The white matter, on the other hand, was still present and looked as if broken off from the cortex. In some places the destruction entered the white matter for a very small distance, but in no place were there the typical wedge-shaped foci that are so common in arteriosclerosis. Nearly all the vessels in the pia were normal, but one artery, just visible with the naked eye, was occluded by an organized, partly canaliculized thrombus.

A typical picture of the area of destruction is given in figure 5. The pia was not thickened or much infiltrated; it contained a great number of large normal vessels. The molecular layer was densely filled with glia cells, mostly astrocytes with a large protoplasmic body and many processes. Some larger vessels perforated this layer, but capillaries were sparse. The external granules were absent in most places, but were present in two small bands of tissue running down through the softened layer of the upper pyramidal cells. This softened area occupied the whole depth of the third layer, but ganglion cells were absent throughout. There was abundant capillary proliferation, but no free phagocytic cells were found. It

Fig. 4 (case 2).—Section through the occipital lobe. Weigert-Pal stain. In *a* the cortex still contains myelinated fibers; in all other places the cortex is softened, but the white substance is normal; × 2.

is characteristic that no fatty granule cells were found in the softened area. The deeper cortical layers had preserved their coherence, but all the ganglion cells had disappeared, and glia cells were not so numerous as in the upper layer. Proliferating blood vessels formed the main features; these increased in number the deeper one went. Between them lay astrocytes and microglia cells, the latter being more numerous in the deeper part. The lowest cortical layer was filled with various cells, of which microglia cells formed probably the larger part. The layer of subcortial tangential fibers (U-fibers) was probably also involved in the destructive process.

This picture was taken from the lateral wall of a fissure. The process, however, was not everywhere equally severe, though no definite rule about the distribution could be given. Nowhere was there softening of the entire cortex in all its layers, and the process was always more marked in the third layer than anywhere else. The white matter was not entirely free, but contained some small

foci of dense cellular infiltration. In some of these, pigment-carrying phagocytes were found; in others, glia proliferation was the main feature.

In other parts of the brain there was not as extensive destruction as in the occipital lobes. One small cortex block showed 5 small intracortical foci, and two small scars in the adjacent white matter. Thrombosis of the hyaline vessels could be seen in one of the cortical foci, but the vessel wall itself (it concerned a feeding cortical artery) was normal. The pia vessels covering this place did not show any changes. Similar thrombosis was not found in the other foci; I do not think that it constituted the primary lesion, but it was probably secondary to stasis and undernourishment of the vessel wall after the focus had been formed.

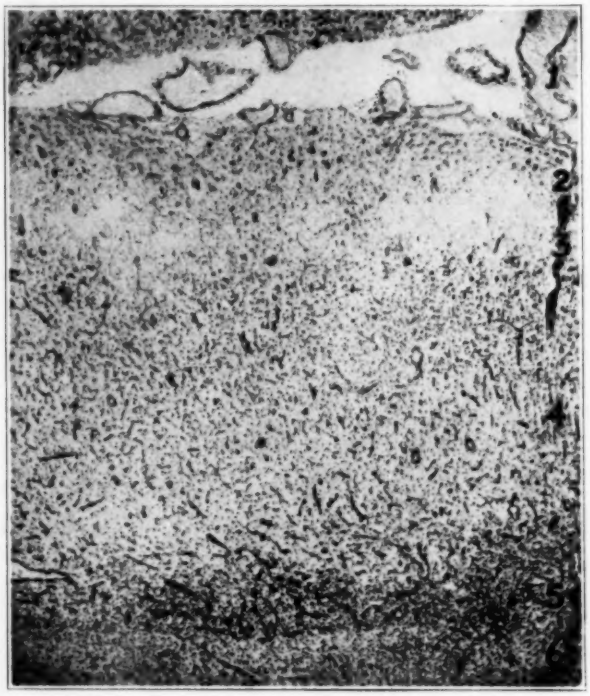

Fig. 5 (case 2).—Cortex in necrotic area: *1*, the pia; *2*, the superficial layer with astrocytes; *3*, the outer granular layer, which has partly disappeared; *4*, the third to the fifth cortical layers, necrosis of the ganglion cells, reaction of the blood vessels; *5*, the lower layer of destruction; *6*, the white matter, with secondary fiber degeneration and glial reaction.

A small hemorrhagic focus in the point of the temporal lobe was cut in serial sections, after paraffin embedding, to study the relations between the blood vessels and the focus. One of the main divisions of the fifth branch of the middle cerebral artery showed endarteritic new-growth on part of its wall. Continuing, a thrombus was seen, developing partly on its new-growth and peripherally to this, finally occluding the entire artery, also its two branches. After some distance the thrombus, which was organized in one part, ended without spreading into smaller branches. The nerve tissue showed a great many ring hemorrhages, which

were evidently very recent as the red blood cells could be seen clearly in the tissue (fig. 6). Many of these lay around a smaller artery, which formed the center of a necrotic mass. In some of these arteries, and in other arteries there were hyaline thrombi. All arteries radiated from a shallow fissure on the surface, in which lay an irregular mass of tissue, probably an organized, thrombosed vessel, surrounded by a great number of lymphocytes. The thrombi first described were continuous from the hemorrhages to the pia, but I do not think that they were connected with the old thrombus, as this was probably lying in a vein. Nor did I find any connection with the thrombosed larger artery, already described. No other foci of softening existed in this hemorrhagic area.

Fig. 6 (case 2).—A fresh focus of petechial hemorrhages in the temporal lobe. Note the thrombosis of the vessels in the pia and brain (black), the infiltration in the pia and the organized material.

On microscopic examination of the thrombosed pial veins in the parietal region, a beginning organization without any signs of inflammation was observed. This evidently was a rather fresh process. An older softened area lay in the cortex, where active repair phenomena were under way.

Comment.—In the beginning of the fifth month of pregnancy, symptoms of a toxemia of pregnancy or uremia developed: edema, nausea, vomiting and convulsions. The patient had acute damage to renal func-

tion, a high blood pressure, fever and stupor. Artificial abortion was performed, and both the uterus and the abdominal wounds became slightly infected, with a progressive fibrinopurulent peritonitis. The kidney symptoms improved, and the blood pressure after delivery was not much above normal. But paralysis of both lower extremities and the right arm and severe general brain symptoms developed. At autopsy, no evidence of a bacterial endocarditis was found. With progressive anemia and continuous high fever, the condition became worse and the patient died of an intercurrent streptococcus cellulitis, six weeks after she first noticed edema of the legs, and four weeks after the attacks of eclampsia.

The focal lesions formed the most important change. There was no sign of encephalitis in the sense of epidemic or allied forms. The focal lesions could be classified into old and fresh ones, the latter being few and consisting of thrombosis of cortical veins, fresh ring hemorrhages due to hyaline thrombi in cortical arteries in the temporal lobe and hemorrhages in some of the older lesions. Of the latter, mention must be made of some endarteritic changes that were probably older than the clinical disease in the patient. The thrombosis of the fifth branch of the middle cerebral artery may have been about four weeks old. Softening was essentially confined to the cortex, where it occupied large areas in both occipital lobes and smaller areas in other parts. No vascular disease was found to account for these lesions. Arteriosclerosis was not present. No wedge-shaped foci of arteriosclerosis were found.

CASE 3.—*Epidemic encephalitis. Coma, then hemiplegia. Gradual improvement. Sudden death after eight weeks. Encephalitis in the brain stem; laminated cortical softening in the right hemisphere.*

Clinical History.—On August 7, a foreigner, aged 29, complained of severe headache and vomiting after being out in the sunshine for a whole day. On the next day he made the same complaints, and the temperature rose to 39.6 C. (103.1 F.). On the next day he was slightly stuporous, and the temperature was 41 C. (105.8 F.). From then on there was rapidly increasing coma, sometimes with a delirious state.

Examination.—When the patient was admitted to the hospital on August 9, a blurring systolic murmur was heard over the heart; the spleen was not enlarged. A white blood count showed 10,500 cells; the blood formula was normal. The urine contained no albumin. The blood pressure was 124 systolic and 82 diastolic. There were no symptoms of meningitis or of hemiplegia. The spinal fluid was clear; the pressure was 230 mm.; the fluid contained some red cells (200 per cubic millimeter) and 30 white cells. Protein was not increased. The eyegrounds did not show changes. There was no paralysis of the eye muscles; the pupils reacted to light.

Course.—On August 12, it was found that the left limbs were not paralyzed, but they were moved only to resist interference. On August 14, the paralysis of

the left arm and leg was definite with extensor plantar reflex and achilles clonus. The face was not involved. Coma had changed to somnolence.

On the next day consciousness cleared up a little, and the patient became able to swallow but not to speak. The left limbs remained very weak, but the Babinski reflex disappeared. The eyeballs acted conjugately when the patient was aroused, but diverged as soon as he was left to himself.

Some further improvement was noted; the patient became able to speak a few words. The temperature had gradually decreased nearly to normal. The white blood count remained between 10,000 and 12,000. Blood cultures had been negative at the beginning, and remained so during the course of the disease.

The Wassermann reaction of the blood and spinal fluid was negative.

The patient was discharged on September 12, and seemed to be improving gradually. On October 1, he had an attack of tachycardia; he died the next day, evidently of heart failure, being conscious until the last. The illness had lasted exactly eight weeks.

Autopsy.—This was performed twenty-five hours after death. The general examination showed cardiac dilatation, edema and congestion of the lungs, decubitus ulcers and scars of older lesions that had no bearing on the present illness.

On macroscopic examination of the brain the dura was found to be normal. The external fluid was slightly increased, and there was hyperemia of the pial vessels. The meninges were a little cloudy, both on the convexity and at the base of the brain, but there were no signs of meningitis. On cross-section the ventricles were not enlarged, and the ependyma and the choroid plexus were normal. The arteries of the brain were not sclerotic. No thrombosis of the veins could be found. The substance of the brain showed multiple areas of softening. The cortex of the right hemisphere was softened in large areas in the frontal lobe as demonstrated in figures 7 and 8. The destruction involved partly the anterior central convolution and spread irregularly to the frontal lobe, as well on its lateral as on its medial surface. The base, however, was free. Softening was generally more marked in the fissures than on those parts of the cortex lying near the surface. Except for very small foci, the underlying white matter was free from changes. As the illustrations indicate, the distribution of the lesion was in the region of both anterior and middle cerebral arteries. The temporal lobe was free from these changes. In addition to this large area, there were smaller softenings in the right hemisphere, in the thalamus, in the anterior part of the putamen and in the head of the caudate nucleus. The left hemisphere did not show softening in the cortex, but here too were foci in the thalamus and in the head of the caudate nucleus. These foci were larger than those in the right hemisphere. Cross-sections through the brain stem showed macroscopically an elective softening of the substantia nigra on both sides. No other areas of softening were found in the lower structures.

Microscopic Examination.—The cerebral cortex showed in the unaffected parts a general loss of ganglion cells, irregularly distributed over the various layers. There were some lipofuscin deposits in the meninges or along the vessels. In several places, however, there was definite widening of the perivascular spaces, which contained a great number of phagocytes. In some instances, most of these were small lymphocytes. Around other vessels there were also plasma cells. Sometimes the same picture could be seen in the pia. The white matter was also edematous, but lymphocytic perivascular rings were not so marked as in the gray matter. Some parts of the cortex contained small foci of softening with intensive glial reaction and ganglion cell degeneration. In some of these foci again were

mild perivascular lymphocytic infiltrations. The larger vessels were normal; they did not show arteriosclerosis, and I did not find thrombosis in any one of them.

The cortex of the softened area showed several layers: First there was a layer of dense glial reaction and larger astrocytes, occupying the original molecular layer. Then followed a small, dense layer of tissue. The whole deeper part was formed by a large number of fatty granule cells and newly formed capillaries together with débris. This pathologic tissue stopped rather suddenly where the white matter began. The larger perforating vessels of the cortex were patent and sometimes had thick sleeves of cells, most of which were plasma cells

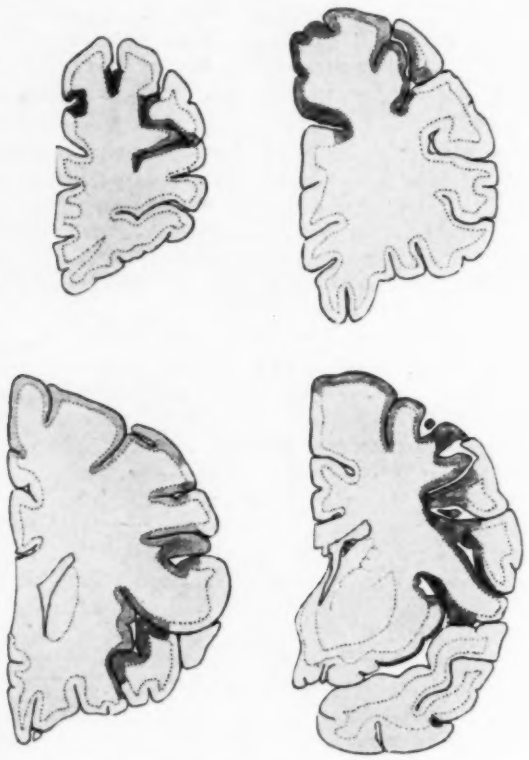

Fig. 7 (case 3).—Four drawings of the right hemisphere. The shaded areas are those of necrosis. This is confined to the cortex.

and fatty granule cells. In the adjacent white matter, considerable secondary degeneration of nerve fibers could be seen, but here in some places there was small cell infiltration around the vessels. The process described was more serious in those places where the superficial cortical layer had disappeared. Its transition into normal tissue was gradual; foci of softening were to be found at a considerable distance from the place of origin. The blood vessels in the pia were all normal.

Several times the softening was more or less limited to the third cortical layer. Here the lower layers, or even the deeper part of the third layer, still showed their ganglion cells; the upper layers, however, had lost the nerve cells, which were replaced by glia cells.

The distribution of the lesion can be seen from figures 7 and 8. It is evident that the cortex in the fissures was much more destroyed than on the surface. There were also some small patches in the temporal lobe.

In some parts of the cortex there were sleeves of small lymphocytes around the blood vessels which probably represent a sequela of the encephalitic infection.

The lesion in the optic thalamus showed the picture of a softening with massive fatty granule cell infiltration and capillary production. However, a great number of ganglion cells with well formed protoplasm and typical nucleus were scattered between the phagocytes. It is therefore evident that the process initially was not

Fig. 8 (case 3).—The fourth slab drawn in figure 7.

a total liquefaction. Around the vessels were thick rings of plasma cells and fatty granule cells. Pigment was rare in this focus. In several places the glia reacted in the form of astrocytes or swollen microglia cells, but many degenerated glia cells could also be found. There were no polymorphonuclears and only a few small lymphocytes in the tissue. The transition from this focus to the normal part was gradual, no wall of connective tissue and glia fibers having been formed between the two parts.

Around the larger vessels in the confines of the focus a small cell infiltration began, and this was also found in the normal parts of the thalamus and in the globus pallidus, the internal capsule and the caudate nucleus. The latter had lost some of

its ganglion cells; the globus pallidus also had lost a great number of its cells, some of which could still be found as dark shrunken clumps.

A section through the mesencephalon showed isolated softening of the substantia nigra (fig. 9). Only in the medial and the lateral corners of this nucleus were there groups of large ganglion cells. The other part of the main nucleus consisted of scar tissue with many plasma cells and fatty granule cells and a few isolated ganglion cells. Thick sleeves of small lymphocytes surrounded the vessels. The ventral parvicellular part of the substantia nigra was in much better condition, although diffuse infiltration with glia cells was present even here. The other structures—red nucleus, geniculate body, etc.—were normal, but sleeves of small lymphocytes around the vessels were present everywhere, and there were also occasional foci of glial infiltration. A lower level section showed these glial

Fig. 9. (case 3).—Substantia nigra. *1*, granule cell infiltration in the substantia nigra; *2*, blood vessels with rings of lymphocytes; *3*, preserved large ganglion cells; *4*, vessels surrounded by fatty granule cells.

proliferations and perivascular changes also in the pons. The oculomotor nuclei were normal.

The cerebellum did not show important changes; there was one glia nodule in the molecular layer of the same type as are found in various forms of encephalitic and other acute diseases of the brain. The most interesting change in the medulla oblongata was a marked atrophy of the large cells of the inferior olives. Several convolutions of this organ were totally void of these cells; in their place was a sclerosis with increased glia nuclei. One or two vessels still carried sleeves of small lymphocytes. In the spinal cord also this type of perivascular infiltration was present, especially of the larger vessels in the dorsal median septum. No definite changes of the anterior horns were noted.

The vessel walls in several places of the nervous axis were partly hyalinized, and thicker than normal. Fat stains also showed often some deposit of fatty substances in the cortical arteries, pointing to vessel degeneration.

Comment.—Headache, progressive coma and high fever developed in a man who had been exposed to the sun. The spinal fluid showed a high pressure. There were no signs of meningitis or of apoplexy. The picture resembled that of encephalitis. On the seventh or eighth day, a left hemiplegia developed, which gradually improved afterward. From then on there was a gradual improvement; the acute stage passed and the patient got up, but a certain weakness of the left limbs remained. He died suddenly in an attack of tachycardia, eight weeks after the onset of the disease. The tachycardia had probably not been present until the day before death.

There were two types of lesions in this brain: encephalitic infiltrations and areas of softening. The encephalitis was localized in the deep gray structures, but slight lesions existed also in the cortex. They consisted of perivascular sleeves of small lymphocytes and foci of microglia proliferation in the white or gray matter. There was also diffuse and rather extensive degeneration of ganglion cells in the cortex and marked degeneration in the inferior olives.

The softening was localized in the gray matter only: the cortex of the right frontoparietal lobes, right caudate nucleus, putamen and thalamus, and the substantia nigra on both sides. A typical encephalitic glial reaction was absent in these foci, but in the substantia nigra the vessels showed sleeves of small lymphocytes. Ganglion cells were often found between the granule cells of the softened areas. There was no wall of vessel and glial reaction around these foci, such as is found in most arteriosclerotic softenings. The arteries were not sclerotic.

CASE 4.—*Gunshot wound followed by severe shock. Infection of wounds. Septicemia. Death after six weeks. Hypertrophic meningitis; one encephalomalacic area in the left insula; laminated softening of the gray matter around the parietal operculum and in the depth of the interparietal sulcus.*

Clinical History.—A Russian soldier suffered from a gunshot wound which caused a fracture of the left humerus; it healed slowly without bony union. The white blood count, however, remained at about 15,000. Six weeks before death, a shell exploded close to him. He had several skin wounds and penetrating wounds of the chest and right axilla. The wounds were infected and discharged freely. The patient developed peritonitis, pleuritis and later septicemia. After the explosion of the shell, he bled profusely from several wounds and was in a state of severe shock. The blood pressure in the right arm did not register (the left arm was in a plaster cast). The pulse was threadlike and its rate from 96 to 220. The patient was cold and clammy, but conscious. The tendon reflexes were normal; a suggestive positive Babinski sign was noted, but no note was made as to whether this was unilateral or bilateral. Under saline infusion the general shock became less marked, but on the day after admission the pulse in the right arm still could not be

obtained. No mention is made in the history about the mental condition, speech or motor power of the extremities. After removal of a pleural exudate the patient improved a little, but he gradually became worse and septicemia developed. The temperature was very irregular, generally between 38 and 40 C. (100.4 and 104 F.) in the last weeks, and the patient died of a general infection. I received the impression from the history that the cerebral insult occurred before or shortly after the patient's admission to the hospital. The poor general condition was probably the reason why neurologic symptoms were overlooked. The patient had not had syphilis. His history before the shell explosion was without significance, except for a gunshot wound causing a fracture of his humerus.

Autopsy.—This was performed twelve hours after death and showed: a subdiaphragmatic abscess around a shell fragment, a partially organized empyema on the right side, an empyema on the left side, fibrinopurulent pericarditis, purulent bronchitis, a splenic tumor, doubtful early acute diffuse granular nephritis and beginning lobar pneumonia with edema of the lungs.

The brain on macroscopic examination showed thickening of the meninges at the convexity. The left hemisphere was white, whereas the vessels of the right hemisphere were injected. No embolus or thrombosis of the arteries was found. On cross-section several encephalomalacic foci were found. With the exception of one focus in the interparietal fissure of the right hemisphere, these all lay in the territory of the left middle cerebral artery. A nut-sized focus occupied the superior border of the insula, involving the claustrum and the inner lamella of the temporal operculum. The external capsule was free. The other softening consisted macroscopically of small dots occupying the lower cortex layers for a stretch of several centimeters in the parietal operculum in its inner and superficial part. There was also a laminated softening in the angular fissure. Small foci of softening were also found in the white matter below these convolutions. The focus in the right hemisphere occupied the deeper cortex of part of the interparietal fissure. There was a sharp margin to the white matter, which seemed normal. However, a streak of secondary degeneration of fibers could be followed in a frontal direction for nearly 2 mm.

Microscopic Examination.—The main feature of this brain was the softening which occupied irregularly the cortical gray matter and sometimes extended a short distance into the white matter. The insular surface of the parietal operculum showed places in which all the layers of the cortex were destroyed and others in which the deeper layers had suffered more than the superficial ones. Destruction often went as far as total softening, including the superficial layer and marginal glia. Intensive phagocytic infiltration and blood vessel formation were the chief features in this area, in which lipofuscin was found in a great number of phagocytes. There was nearly always a wall of granulation tissue between the affected cortex and the white matter; outside of this wall were astrocytes and phagocytes as signs of a secondary degeneration of nerve fibers. The margin between affected areas and normal cortex was often very sharp and without much reaction.

In one part of the cortex, adjacent to a small focus occupying all the cortical layers, the ganglion cells were well preserved; some of the long perforating arteries here showed marked endothelial and adventitial proliferation. This was not noted in the short intracortical arteries or in the capillaries. The pia and underlying granulation tissue formed one inseparable mass in the most affected areas. In the other parts in which the glia of the superficial layer still persisted, the pia did not show many changes, but it was infiltrated with many phagocytes. In one part of the parietal lobe, softening had occurred essentially in the

fifth and sixth cortical layers for a distance of several centimeters (fig. 10). Here there was a mild glial reaction in the superficial layer; ganglion cells were present in the second, third and fourth and part of the fifth layers, some of which had no more processes; others, however, were shrunken. Their number was not much decreased; there was no evidence of neuronophagia and not much increase of small glia cells. Instead of the nerve tissue in the fifth and sixth layers, or in some places the lower half of the fifth and the sixth layer, there was granulation tissue consisting of a great many newly formed blood vessels with fatty granule cells, some plasma cells and probably a few fibroblasts. This tissue did not contain any ganglion cells or glia. Below this layer no ganglion cells were present, and one saw the striped structure of the white matter (fig. 11).

Other foci showed that the elective softening was confined entirely to the lower part of the cortex, without involvement of the white matter. It is interesting to state that the ganglion cells in the higher levels, the axons of which must have been destroyed at the onset of the disease, were still in fairly good condition

Fig. 10 (case 4).—Laminated softening in the parietal lobe, occupying the fifth and sixth cortical layers only, except in the central part of the picture where the other layers are also affected. *1*, first to the fifth layer; *2*, softened lower cortex; *3*, white matter, with secondary edema.

(fig. 11). Myelinated fibers were not found in the softened layer, but the sections gave me the impression that some fibers must have grown into it secondarily without, however, perforating into the upper part of the cortex. A few medullated fibers were still found in the preserved parts of the cortex.

In the affected part of the parieto-occipital fissure there was a condition resembling more that described in case 3; an isolated laminated softening of the second and third layers. The first layer was represented by large astrocytes; but the nerve and glia elements of the underlying cortex had disappeared and were replaced by granulation tissue. Some large pyramidal cells of the third layer, however, were still present, and the fourth, fifth and six layers retained their architecture.

The blood vessels in the pia were all present. There was no evidence of thrombosis or endarteritis of the smaller vessels in the fissures or on the surface.

There was no small cell infiltration nor evidence of any glial reaction typical for encephalitis, but in some vessels the media was thickened. There was, however, in one large softened area, a patch of not quite fresh hemorrhage around a thrombosed artery. This was the only evidence of organic disease of the blood vessels in the affected area that I was able to find.

In those parts of the cortex not directly affected, there were no typical changes. There was a moderate degree of ganglion cell degeneration, but not more than could be expected in death following septicemia. The pia was a little thicker than usual, but was not infiltrated. The basilar and carotid arteries contained small places with endarteritis, however, without thrombus formation. The Ammon's horn showed a change in the cells of the gyrus hippocampi near the border of the Ammon's horn pyramids. The cells were much smaller and lay closer together than in normal parts. The surface was sunken in; there was an increase in

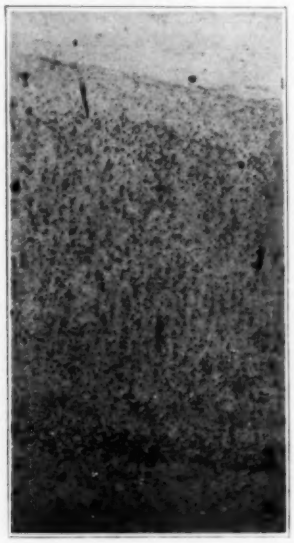

Fig. 11 (case 4).—The same cortex as is shown in figure 10; higher magnification. *1,* more normal cortex; *2,* line of softening in fifth and sixth layers; *3,* white matter.

marginal glia, but no increase of the glia between the ganglion cells. The latter still had their pyramidal shape; the nucleus was dark and generally only half the size of a normal nucleus, but with a distinct nucleolus. No vascular reaction could be seen. This process occupied the upper layers in a more severe degree than the deeper layers, but in one place the entire depth of the cortex was involved. No changes in Ammon's horn comparable to the sclerosis found in many conditions and attributed by Spielmeyer to functional disturbance of circulation were found.

Comment.—A soldier, who probably had had an infected compound fracture of the humerus for some time, was wounded by shell explosion and remained in a condition of considerable shock, without measurable blood pressure for nearly a day. Gradual recovery took place, but an

infection of the wounds developed, with ultimately septicemia. Weakness of the arm or the face was noted, probably because of the severe wounds. The patient died of septicemia six weeks after the shell explosion. Examination of the brain showed laminated softening in the cortex in various parts of the territory of the left middle cerebral artery and in a small area of the right hemisphere. In the insula some subcortical matter was also involved. In some parts the softening was limited to the fifth and sixth layers of the cortex only. No apparent cause in blood vessel disease or inflammation could be found.

REVIEW OF THE LITERATURE

The four cases described had two important points in common: 1. The softening was nearly exclusively localized in the gray matter, and in cases 2, 3 and 4 took the form of laminated necrosis. 2. No organic change in the blood vessels could be found to account for the necrosis. It is true that thrombosis of smaller arteries occurred, especially in case 1, in the foci of necrosis, but these foci were larger than the area supplied by the affected artery. The most probable explanation, therefore, is that the vessel wall was damaged by the same process (ischemia) that caused necrosis of the nerve tissue, and that thrombosis occurred as a result of the damage done to endothelial cells.

Ischemia of the nerve tissue (including stasis and prestasis in the sense of Ricker) is the most likely explanation of the changes described. A toxic degeneration of the ganglion cells is not probable, because the process was not elective in all cases and the presence of a toxin was very improbable in the last case. Vogt's theory of pathoclisis does not hold good for this group of cases, as has been proved by many authors (Hiller, Spielmeyer, Neubürger, and others). Ischemia must act more powerfully on the gray matter than on the white, causing necrosis of the first while the latter can still survive.

It does not seem likely that primary edema of the brain could cause a degree of ischemia leading to necrosis of the cortex in the distribution described. It is known that swelling of the brain in carbon monoxide poisoning takes place by means of a force much greater than blood pressure (Forbes, Cobb and Fremont-Smith), but this is a much more general process and produces, in earlier stages, venous congestion without ischemia (for the rôle of venous congestion consult the discussion of Ricker's peristasis). Simple venous congestion, for instance, in sinus thrombosis does not show the pathologic changes that I have described; it is known that it can give rise to necrotic areas, but hemorrhage is always a concurrent feature, and these foci do not show any preference for the gray matter.

As possible causes for the ischemia one must discuss vessel spasm and lowered blood pressure through systemic disease.

Direct Evidence of Vessel Spasm.—It is generally accepted at present that nerves are present in the arteries of the pia and the brain. These nerves have been demonstrated anatomically and experimentally (see the excellent résumé of the literature by Forbes and Wolff). They can be stimulated locally by various kinds of stimuli (Cushing, electrical; Florey, mechanical, electrical, chemical; Forbes and Wolff, electrical).

However, no uniform opinion exists as to the irritability of pial vessels to stimulation of the cervical sympathetic. Florey (1925) was not able to see a change in the caliber of pial vessels from stimulation of the sympathetic trunk, and he therefore denied "the presence of any nervous control over the caliber of the cerebral vessels." But this may be due to a defect in his technic, since Forbes and Wolff (1928) found that stimulation of the sympathetic was followed by constriction of the arteries of the pia, stimulation of the vagus by dilatation of those vessels. According to Meagre and Ingram, stimulation of the cervical sympathetic never leads to anemia of the brain, causing coma or convulsions. Cobb (1929), in experiments with Talbott and Wolff, was able to demonstrate that after section of one cervical sympathetic nerve the length of open capillaries in the cerebral cortex increases from 12 to 49 per cent in different areas.

The regulation of the caliber of the pial arteries is complicated: Change in venous pressure, change in arterial pressure and change in spinal fluid pressure influence the flow through the vessels directly and sometimes by reflexes on the vasomotor nerves. The chemical constitution of the blood (osmotic pressure, drugs, viscosity) may have an influence, and one knows that mechanical stimulation may have a marked and sometimes lasting effect on the lumen of the artery (Florey). The pial vessels participate in general changes in vascular tone during mental exaltation (Braunmühl). One need not go into further details here; it is sufficient to conclude that vessel nerves exist in the pia, and that these nerves can be stimulated or paralyzed as well by local as by general stimuli.

No evidence has been forthcoming, as far as I am aware, of the simultaneous occurrence of dilatation of the arterioles and capillaries with contraction of the smaller arteries (the postulated condition causing Ricker's peristasis). Bouman (1928) mentioned that isolated spasm of smaller cerebral vessels is improbable according to physiologic knowledge of vasomotor innervation.

According to Kennedy (1923), direct evidence of spasm of pial vessels is also given by his interesting observation of blanching of the cortex during the first moments of an epileptic attack, followed by venous engorgement as the tonic stage lasted and passed into the clonic stage.

Of much less importance is the clinical evidence of vessel spasm. It has long been recognized clinically that spasm of arteries occurs and can give rise to transitory symptoms. Raynaud, as early as 1862, explained the syndrome which bears his name by disturbances of capillary innervation. Pal developed his theory of vessel crisis in tabes, and Oppenheim described intermittent claudication, for which he held congenital smallness of the arteries, sclerosis and spasms responsible. It is also an old theory that many transitory symptoms in eclampsia, uremia and migraine, as, for instance, hemiplegia, aphasia and amaurosis, are due to spasm of cerebral vessels. It sometimes happens that symptoms that were transitory before become persistent. In some of these cases no obstruction of the arteries has been found to account for the defects (Foix).

The clinical discussion bears mostly on large syndromes and large anatomic lesions of the size and type of the common arteriosclerotic lesions. They do not resemble the laminated defects described. This point may be of great importance, because one will then have to find out under what circumstances the defect remains confined to the gray substance.

An observation of Osler (cited by Kennedy) seems to confirm the theory that convulsive attacks are due to, or at least ultimately caused by, a spasm of cerebral arteries. He observed a patient in whom convulsions and Raynaud's syndrome always appeared together during the cold season.

Not much attention has been paid to the causes of spasm of cerebral vessels. It is generally accepted that the toxin circulating in the blood in uremia and toxemia of pregnancy can cause spasm of the vessels. Endocrine disfunctions sometimes probably play the same rôle, and in hypertension, injury to the skull (Friedmann, 1897) or mental exaltation (Braunmühl, 1928) one can think of disturbances of vasomotor reflexes; but not sufficient experimental work has been done to give a clear idea about these conditions. Chronic lead poisoning, which one admits may cause spasm of the vessels, seems to be of no importance in the cases under discussion.

Before discussing the pathologic evidence of functional ischemia as a cause of brain defects, Ricker's theory of peristasis (1919) calls for a short discussion. Ricker called "peristasis" the condition in which spasm of the arteries occurs together with a dilatation of the arterioles and capillaries. Further, he stated that during the normal flow of the blood the walls of the arteries and capillaries have, under nervous control, a direct propelling action on the blood. In the peristatic condition this action is absent, according to Ricker, and the flow of the blood is very slow (prestasis) with ultimate stasis.

During a spasm of the arteries, the nerve tissue will become more or less anemic, and then a dilatation of the capillaries (and precapillaries) will cause the blood to flow more slowly, but the total amount must be increased (less resistance), and the surface through which absorption may take place is also increased. It is therefore difficult to conceive why this peristatic condition gives rise to ischemic necrosis, as Ricker assumed, unless one supposes that the capillary dilatation is irregular or is even absent in some parts of the arterial region. All the blood will then pass through the dilated parts, and one will find total stasis with ischemic necrosis in the nondilated capillaries (Hiller).

I may recall in this connection that Martin and Brooks (1923) demonstrated that in ischemia from a lesion or ligation of an artery in the leg (dog or man), venous stasis by ligation of the femoral vein could prevent the threatening ischemic necrosis. Venous stasis, therefore, is not necessarily disadvantageous to the tissues. Another argument against the importance of Ricker's theory is Braunmühl's observation of lesions of the brain in eclampsia. He found microscopic changes typical of ischemia without any signs of stasis.

In pathology, two main questions form the object of researches in this field in the last decade. Are the small lesions in the form of necrobiotic or necrotic foci in the gray matter, as found in arteriosclerosis, carbon monoxide poisoning, etc., vascular in origin? If they are vascular, can they be caused by functional disturbances of the circulation (local spasm or general fall of blood pressure)?

Vogt, in his theory of pathoclisis (1922), suggested that small lesions, localized for the larger part in the third cortical layer, are due to an elective vulnerability of the affected parts without any influence of vascular distribution. Against this theory, Neubürger described the same type of lesions in fat and air embolism, in which the vascular origin is obvious.

Hiller, Westphal and Jaffé described the same lesions in carbon monoxide poisoning and eclampsia, and were able to show that, here again, vascular changes are the primary process. Spielmeyer made a thorough investigation of the sclerosis of the Ammon's horn in epilepsy and many other diseases, and demonstrated that a vascular lesion must be the cause. He reached the conclusion that a spasm of the smaller arteries during an epileptic fit or during other diseases of the brain (meningitis, etc.) caused necrobiosis of the cells of the sector of Sommer in the Ammon's horn. Hiller and Jaffé also emphasized the functional character of the vessel changes.

Similar lesions have been known for a long time in arteriosclerosis, in which the vascular origin is apparent, but they were attributed to organic changes in the diameter of the vessels. It seems probable,

however, that the mechanism is more complicated and that spasm (Westphal) or low blood pressure (Sträussler and Koskinas) plays an important rôle in the ultimate causation of the foci.

I will not discuss massive hemorrhage and malacia, but there is reason to believe that in these processes, as well as in the smaller lesions, functional changes in the diameter of the small arteries are important for the development of secondary hemorrhages and necrotic foci.

Influence of Low Blood Pressure on the Origin or Further Development of Encephalomalacia.—The discussion in the literature about the significance of a sudden fall of the systemic arterial pressure is of great interest. In 1925, Brinkmann offered the suggestion that cardiac insufficiency may have played a rôle in the pathogenesis of the foci of laminated softening, although in his final conclusions he did not mention this factor. In the same year, Foix described a case of symmetrical softening of the hemispheres and admitted that, although arteriosclerosis is the cause, the fall of the blood pressure due to venesection may have had some immediate influence. He also suggested the possibility of changes in the viscosity or coagulability of the blood. In the discussion following Foix' demonstration, Vincent laid especial stress on the point in question, and for the first time called full attention to the importance of a decrease in the arterial pressure. He stated that in two patients with arteriosclerosis, venesection had probably been the determining factor of a severe cerebral ictus. After death the arteries were found patent.

Then Fleming and Naffziger (1927) described cases of transient hemiplegia, mostly in aged and sclerotic persons, offering as an explanation a sudden fall of the arterial pressure. Artificial increase of the pressure (drugs, massage, forcing fluids, venous stasis) was followed in their patients by recovery. Therefore they refute the spasm theory that had heretofore been used to explain these cases.

Bodechtel (1928) described a patient with postoperative cerebral disease in whom, during narcosis, the heart stopped for twenty minutes. The patient died fourteen hours afterward, and the brain showed ischemic ganglion cell disease in many areas. Von Braunmühl (1928) also described some cases; his case 4 seems to be conclusive. During an accident, a healthy man had a heavy weight on the thorax, causing asphyxia and heart failure. He showed convulsions and died after six hours. Many ischemic foci were found in the cortex of his brain. Lhermitte (1928) also called attention to the significance of lowered blood pressure as a factor in the pathogenesis of cerebral accidents.

The older literature does not mention laminated cortical loss of cells. The case of Freund, mentioned by Vogt, is not quite typical. Vogt (1922) stimulated the cortex in monkeys and found, as early as two hours afterward, foci with a total absence of nerve cells due to a

cytolytic process, more especially localized in the third cell layer of Brodmann. Vogt explained this observation by his theory of pathoclisis, but in view of recent experimental work I think that contraction of the cortical vessels may have been the cause. Siegmund (1923), in studying cases of birth injury, mentioned that he sometimes found fissure-like cystic defects in the cortex. However, he did not explain their pathogenesis.

It was not until 1925, when Brinkmann called attention to these processes, and 1926, when Neubürger described his cases, that the general importance was seen and the question became one of general discussion. Brinkmann reported two cases with general arteriosclerosis in which he found foci of decortication (Abschälung der Rinde vom Mark). No organic changes in the vessels were present; but Brinkmann did not give an explanation for his observations. Neubürger had described, in 1925, cases of fat and air embolism in which he attributed the laminated loss of ganglion cells partly to obstruction in the pial vessels and partly to vasomotor disturbances. In his paper of 1926, he specified his opinion by attributing the linear softening in cases of general arteriosclerosis to spasm of the smaller arteries and arterioles in the regions supplied by a number of larger pial arteries. He did not think that stasis in the capillaries could explain the picture.

Sträussler and Koskinas described the tapelike atrophy of cells in the third cortical layer, often found in dementia paralytica, which has been attributed to a primary vascular process. They also gave a description of a case of isolated laminated softening of the fourth layer in arteriosclerosis; but this patient showed also foci of classic distribution. No detailed explanation was sought.

The scar of a laminated lesion in the cortex, probably due to an old infantile paralysis, was described by Jakob in 1927. Finally, an interesting case was described by Bodechtel (1928), who saw extensive laminated loss of ganglion cells, especially of the third layer, in a patient who died fourteen hours after a temporary heart failure during narcosis.

COMMENT ON MY CASES

In case 1, toxemia of pregnancy was present, as evidenced by headache, premature delivery, icterus and convulsions; in addition, there was a mild chronic arteriosclerosis of the larger arteries at the base and of smaller intracortical arteries, together with chronic degeneration of ganglion cells. The foci of necrobiosis in the cortex cannot be explained by an organic change in the blood vessels, although secondary thrombosis of arteries in the foci was found in some places. No swelling of the brain was found at autopsy, and as death occurred during the acute stage of the disease it had probably not been present to any

great degree. It is not likely that a simple toxic action by the toxemia of pregnancy caused the necrobiosis, because that theory could not explain the thromboses occurring in the foci nor the fatty degeneration of the vessel walls in other places.

One may therefore assume that the toxin acted on the arteries, causing a spasm which secondarily, through ischemia, caused macular necrosis of the nerve parenchyma and of the vessel walls themselves. The thrombosis probably occurred after the circulation had been restored; the hemorrhages in the necrotic parts occurred also after some circulation was again present. The ischemic nerve cell degeneration, diffusely distributed over the cortex in wide areas around the foci of necrosis, also points to a much wider primary lesion, from which, however, other parts were able partially or totally to recover.

The patient in case 2 had, in the fifth month of pregnancy, an attack of eclampsia or uremia (chronic kidney changes were found at autopsy). After cesarean section the convulsive attacks stopped, and the blood pressure came down to normal. Fever developed, however and probably two days later paralyses were noted. There had not been a period of shock with low blood pressure, but the patient was still semicomatose. It is difficult to decide exactly at what moment the paralyses set in, but it seems certain that they were not present on the first day after the operation. No organic vessel lesion was found to explain the softened areas of the brain, although there were thromboses of various pial vessels in other places. Fresh changes, due to septicemia, were apparent in many places. They were of the usual character: thromboses or small necroses with hemorrhage.

It is difficult to conceive that a vessel spasm-producing toxin still circulated in the body three days after the convulsions had stopped. Neither do I think that this case could be explained in the same way as cases of brain purpura following the injection of arsphenamine. In the latter, as is well established, a common injection of neoarsphenamine is followed on the seventh or eight day by acute brain symptoms, coma and often convulsions, and death occurs rapidly, mostly within forty-eight hours. At autopsy one finds brain purpura which can best be explained by the theory of a primary damage to the capillary walls, caused by the drug itself, and secondary thrombosis of the vessels with necrosis of the nerve tissue and hemorrhage through diapedesis. However, in case 2, although a "preparatory period" of five days was present, one fails to find the thrombosis of the vessels as the expression of primary damage to the vessel walls.

It may be that the reverting of the blood pressure from its initial high value to the normal level played a more important rôle than had hitherto been believed.

In case 3 there was a fulminating encephalitis after hard exercise and exposure to the sun. Some difficulty is encountered in explaining the gradual onset of the hemiplegia on the fifth day of the disease. From the first day, increased intracranial pressure was present, and the coma had been increasing gradually. One therefore can expect either swelling of the brain or a venous stasis, or both, but, as has been seen already, these conditions do not cause necrosis of the gray matter unless aided by general anemia or vessel spasm. It is remarkable that the softening is always more marked in the fissures than on the surface of the convolutions. Here, as in the other cases, the vessel walls were normal. It is not now possible to give an explanation of the pathogenesis of the softening in this case; it will be necessary to wait until similar cases have been observed.

In case 4 no data are available to prove when the softening occurred, but probably this happened soon after the blood pressure fell to a very low level during the severe shock, which lasted for more than a day. The mental shock might have caused an initial spasm of the cerebral arteries, but it does not seem likely to me that this played an important rôle. This case can be compared with the cases of temporary heart failure of von Braunmühl and Bodechtel, and is clinically comparable with the cases of Foix and Lhermitte.

There are still many questions to which the answers cannot yet be given. Is the vulnerability of the gray matter to ischemic necrosis due only to its greater need of oxygen and its greater metabolism, or has the capillary distribution or the vasomotor control some influence on this localizing difference? What is the significance of the laminated type of lesion? Is this due only to factors of vascular distribution and innervation, or must one still look for another factor, a special vulnerability of certain ganglion cells in the sense of Vogt's pathoclisis? Some facts are in favor of this theory, but it is not yet time to come to a final conclusion. The localization, in the majority of the cases in the literature and in mine, has been in the third cortical layer, but in others (Sträussler and Koskinas, my cases 1 and 4) it was different or varied in some places. It might be possible that the momentary condition of the vascular system at the time of action of the disturbing agency plays an important rôle in the localization of the lesions. For, although no exact data are available, one may expect that there are changes in the flow of the blood which accord with the times of rest and function of certain parts of the cortex.

SUMMARY AND CONCLUSIONS

Four cases are described, clinically and pathologically, in which localized brain symptoms were due to elective softening of parts of the cortex and for which no organic vascular lesions could account.

One case shows small foci of necrosis or necrobiosis, distributed apparently without rule over the various layers of the cortex. In the other cases the lesions take the shape known as laminated cortical softening. The latter may destroy the cortex in its entire depth, or (often in other parts in the same hemisphere) may be restricted to one or two cell layers. The third cortical layer is most frequently the seat of this lesion; it was also found in the fifth and sixth layers together. No data have been gathered to account for these differences in distribution.

All the cases show, at the same time, lesions other than those just mentioned, of the common vascular type or thrombosis of vessels in other places, mostly in connection with widespread diffuse degeneration of ganglion cells.

In case 1 a spasm of the cortical arteries, due to toxemia of pregnancy, is the probable cause. In case 4 a sudden and prolonged intense fall of the blood pressure must have resulted in cerebral anemia with localized necrosis. In both the other two cases the cause of the cerebral ischemia was not simple and could not be ascertained satisfactorily.

In these patients predisposing factors have been found, but seem to be of little importance.

From a study of the literature it is evident that the direct cause of spasm of the vessels in human disease is not yet known.

Functional disturbances of the cerebral circulation probably play a much greater rôle in the pathogenesis of foci of softening in general arteriosclerosis than has hitherto been believed.

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HEMORRHAGE OF THE BRAIN*

L. BOUMAN, M.D.
UTRECHT, HOLLAND

There are many different conceptions of the genesis of hemorrhage of the brain. According to Charcot and Bouchard,[1] cerebral hemorrhages are caused by the rupturing of a miliary aneurysm. By carefully washing the lesions, they found aneurysms from 0.2 to 1 mm. in size and visible to the naked eye; these were not only inside, but also outside, the actual focus. According to Charcot and Bouchard, the aneurysms were not caused by arteriosclerosis, but by a diffuse periarteritis with thickening and proliferation of cells of the vascular adventitia and muscularis.

Löwenfeld[2] found that it was chiefly the media that was affected in the center of the apoplectic focus. He called this condition granular degeneration. The muscle fiber swells and becomes more refractive; the nuclei disappear, and the whole mass becomes finely granulated; these granules afterward conglomerate, the refractive power diminishes, and the whole muscular wall may disappear. The adventitia is least affected, but in this layer the nuclei are often increased in number. In the adventitia, cells showing fatty degeneration are often found, also red and white blood corpuscles and occasionally dissecting aneurysms. Löwenfeld considered this a process of diapedesis, for he did not find a rupture of the inner vascular wall.

Pick[3] and Ellis also found Charcot's miliary aneurysms in two thirds of their cases, but in only 13 per cent were they really ruptured. According to them, the fatal hemorrhage took place from one or more larger aneurysms or from a ruptured arteriosclerotic vessel without an aneurysm. To them, arteriosclerosis is the cause of both dissecting aneurysms and subsequent hemorrhages (fig. 1). They called these aneurysms "aneurysmata spuria." Around them is found hardly any reaction of the cerebral tissue, a fact from which the authors concluded that this vascular change occurred just before death.

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* Submitted for publication, June 30, 1930.

1. Charcot and Bouchard: Nouvelles recherches sur la pathologie de l'hemorrhagie cérébrale, Arch. de physiol. norm. et path., 1868.

2. Löwenfeld: Studien über Aetiologie und Pathogenese der spontanen Hirnblutungen, Wiesbaden, 1886.

3. Pick: Ueber die sogenannten miliären Aneurysmen der Hirngefässe, Berl. klin. Wchnschr. **47**:325, 1910.

Rosenblath [4] introduced a new idea; he had found in the earlier French literature an article on apoplexy by Rochoux who had given the following definition: "une hémorrhagie par rupture, suite d'une altération du tissu propre de l'encéphale (a hemorrhage caused by rupture following alteration of the brain tissue)." Rosenblath considered this conception important. Too little notice had been taken of the numerous small hemorrhages so often found near the large lesions. There was

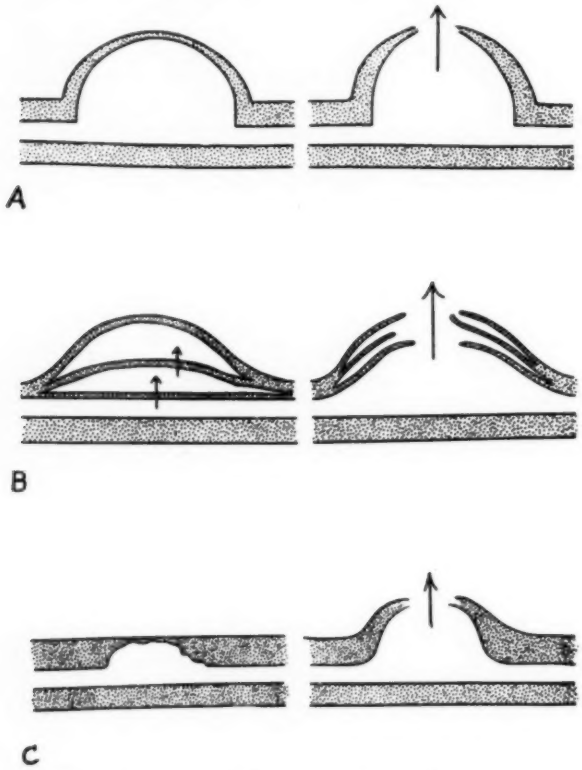


Fig. 1.—*A*, miliary aneurysm (Charcot); *B*, aneurysma dissecans (Pick and Ellis); *C*, atheromatous ulcer (Rühl).

not simply rupture of vessels causing small and infinitesimally small hemorrhages, but these vessels had been subject to a process of necrosis. The tissue between such hemorrhages also shows signs of serious damage. One sees swelling and hyaline degeneration; the nuclei of the muscularis and intima disappear, and even the elastica. The whole vascular wall loses its differentiation into the various layers and becomes homogeneous. The aneurysms of Charcot are found. This process

4. Rosenblath: Ueber die Enstehung der Hirnblutung bei dem Schlaganfall, Deutsche Ztschr. f. Nervenh. **61**:10, 1918.

of arterionecrosis is found exclusively in the region of the apoplectic lesion, not only in the major hemorrhage but also in the small isolated hemorrhages that invariably accompany it.

What is the cause of this process of encephalomalacia? Rosenblath postulated an unknown toxin suddenly attacking a circumscribed cerebral area, in which glia, nerve fibers, ganglion cells, capillaries and veins are all destroyed in a diffuse manner or in patches which subsequently melt together. Some of the arteries escape this process of necrosis, especially those of which the walls have become thickened and resistant

Fig. 2.—*A*, diseased parenchyma causes alterations in the vessel wall; *B*, the altered vessel may burst (Rosenblath). In this and subsequent figures, the altered tissues are dotted.

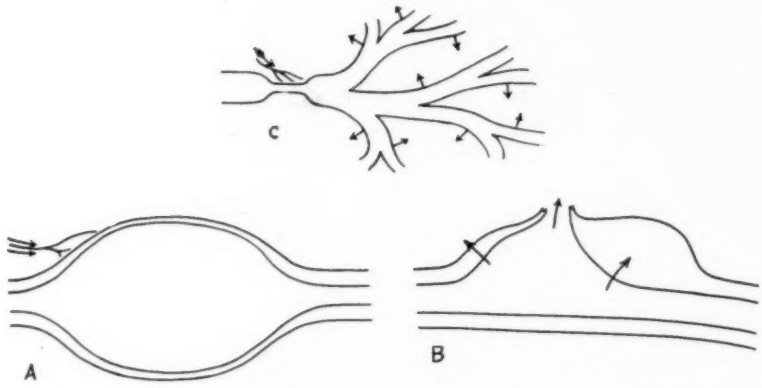


Fig. 3.—*A*, excessive neural impulses may paralyze the vessel wall; the vessel dilates. *B*, if the blood pressure has not decreased, the liquid movement in the wall itself is suppressed. The wall degenerates and the blood may pass through it (Ricker). *C*, neurogenic spasm of an arteriole causes reflex dilatation of its capillaries, stasis and hemorrhage by diapedesis. If blood from the surrounding vessels enters the area of the diseased vessel, a circular hemorrhage is formed (Ricker).

through arteriosclerotic changes. The blood that oozes through the vascular wall under very little pressure is derived chiefly from capillaries and veins (a hemorrhage into the ventricles is unusual). The arteries are often occluded by thrombi. The blood corpuscles do not often suffer from this toxin.

Analogous experiments were performed by Lotmar, who worked with dysentery toxins and was able to cause by that method myelitis and encephalitis, small hemorrhages and progressive and retrogressive changes of the vascular wall. In cases of nephritis one often finds retinal hemorrhages and albuminuric retinitis, and it is in the same cases that one so often sees apoplexy.

The direct etiology of the apoplexy remains unknown; neither the increased blood pressure nor the arteriosclerosis commonly present can

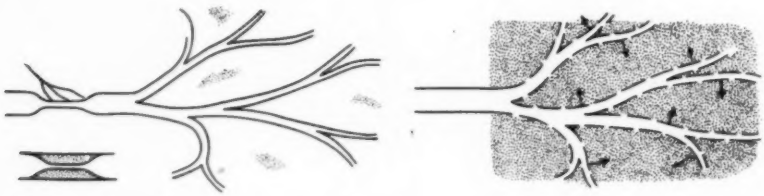


Fig. 4.—*A*, angiospasm, or arteriosclerosis, causes ischemia, followed by necrosis of the nervous parenchyma; *B*, this causes necrosis of the vessel walls; after the spasm has relaxed, the blood reenters these vessels and passes through their altered walls (hemorrhage by diapedesis) (Westphal and Bär).

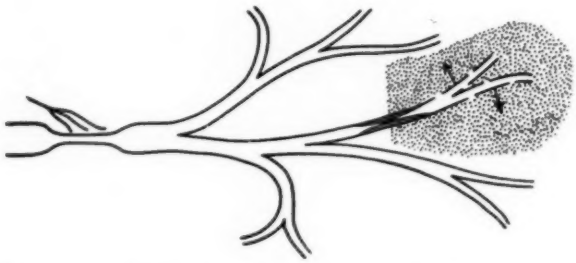


Fig. 5.—Spasm of a large artery (often extracerebral) causes the mechanism of Westphal-Bär in the areas of arteriosclerotic vessels only (Böhne).

explain it. One is compelled to assume that the altered metabolism in a case of nephritis causes certain ferments to enter into the general circulation (fig. 2, *A* and *B*).

Ricker [5] was of the opinion that in certain cases the hemorrhage takes place from an aneurysm or merely from a sclerotic artery without an aneurysm. Another cause of apoplexy is the so-called "arteriohypertonia." An arteriole may be brought to extreme contraction through some nervous influence; consequently the capillaries may dilate maximally in the terminal region. In that case there is stasis and a

5. Ricker: Sklerose und Hypertonie der innervierten Arterien, Berlin, Julius Springer, 1927.

condition called "peristatic diapedesis." The blood flows slowly through the capillaries because of the diminished pressure, and the erythrocytes leave the vessel by diapedesis. In that way, great extravasations may occur, and sequestration necrosis follows with slow destruction by scavenging granular cells (fig. 3 *C*). Moreover, hemorrhage through "dia-eresis" from small arteries and veins takes place as the pathologic changes cause the walls of the vessels to disintegrate.

While this occurs in the same way in other organs, something more occurs in the case of cerebral hemorrhage, viz., necrosis of the muscularis of certain arteries. Nervous stimulation may cause a complete paralysis with the formation of fusiform aneurysms; the blood flows through the paralyzed part under diminished pressure, or in the case of arterial hypertonus, under increased pressure. The vascular walls are compressed, causing necrosis. As the blood pressure is increased,

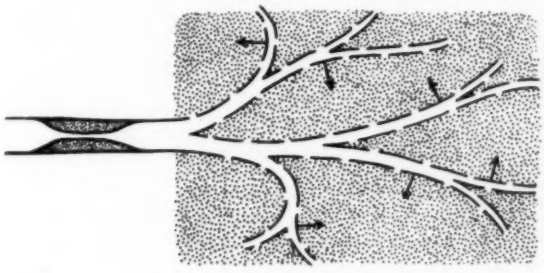


Fig. 6.—Marked arteriosclerotic narrowing causes necrosis of the nervous parenchyma and of the vessel walls. The little blood that flows through the narrowed artery passes through these degenerated vessel walls. If blood from the surrounding vessels enters the diseased vessel area, a circular hemorrhage is formed (de Vries).

rupture of the vascular wall takes place. In some cases dissecting aneurysms are formed. Occasionally the part containing the sequestration necrosis swells and changes into an aneurysma spurium, the blood passing from the lumen of the vessel through its inner walls into its necrotic parts (fig. 3 *A* and *B*).

Westphal and Bär [6] found at the periphery of the apoplectic focus numerous small and minute hemorrhages. These offer a much better opportunity of studying the vascular changes than does the larger central hemorrhage. He noted extensive damage to the vascular wall. There are, however, extravasations into the vascular sheaths of arteries and veins which do not show any anatomic changes. What one finds is

6. Westphal and Bär: Ueber die Entstehung des Schlaganfalles, Leipzig, F. C. W. Vogel, 1926.

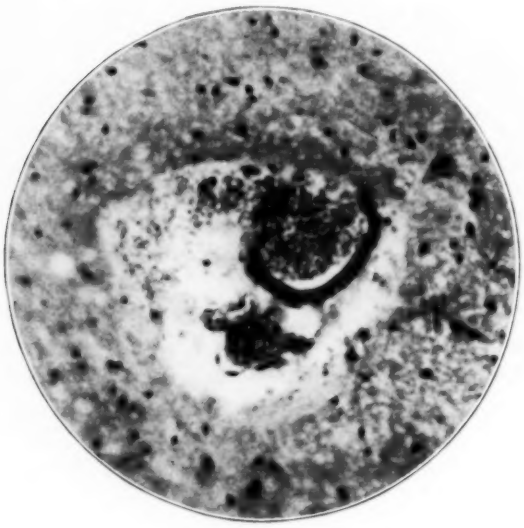


Fig. 7.—Rupture of the wall of a vessel in the area near a hemorrhage. Hematoxylin-eosin stain; × 200.

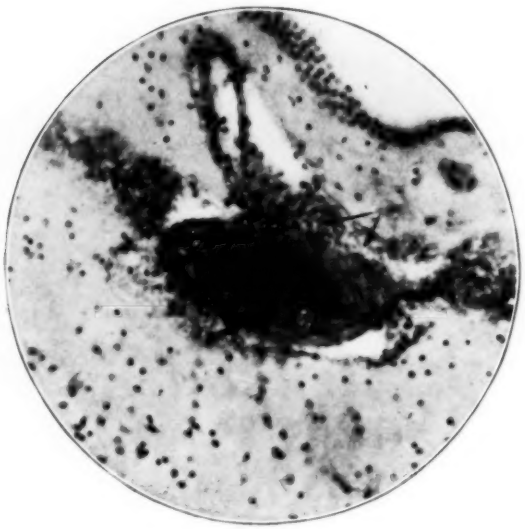


Fig. 8.—Blood in the Virchow-Robin space. Van Gieson stain; × 144.

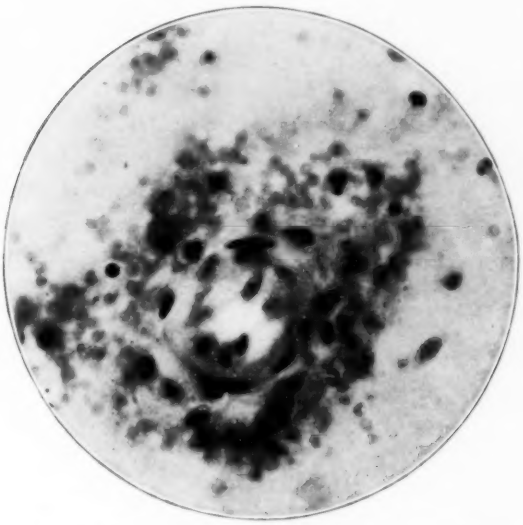


Fig. 9.—Blood in the glia spaces of Held. Hematoxylin-eosin stain; × 450

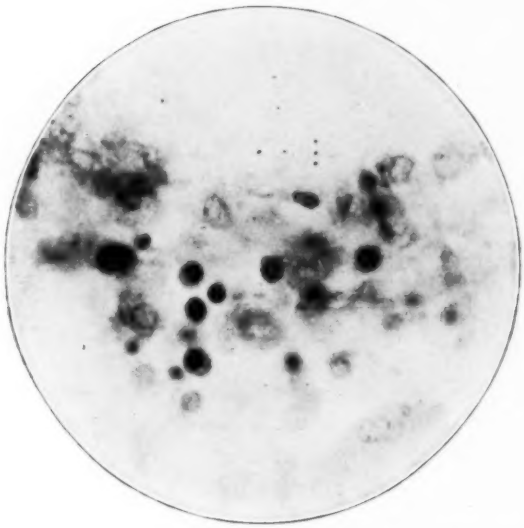


Fig. 10.—Perivascular infiltration (Gewebigzellige). Nissl stain; × 594.

not only sclerosis of arterioles and arteries, but, above all, general angionecrosis in the hemorrhagic area and its periphery, with numerous small hemorrhages. Hemorrhages by diapedesis or rupture from the seriously affected vascular wall are possible. Also, the changes of the veins may be the cause of larger extravasation.

The usual general vascular lesions also occur in cases of combined malacia and hemorrhage. Anemia following thrombosis or arteriosclerotic intima proliferation often causes encephalomalacia; a process of this nature is the most plausible explanation of the general tissue damage that one finds in the case of hemorrhage. One sees a necrosis of both the cerebral tissue and the vessels. Westphal and Bär expressed

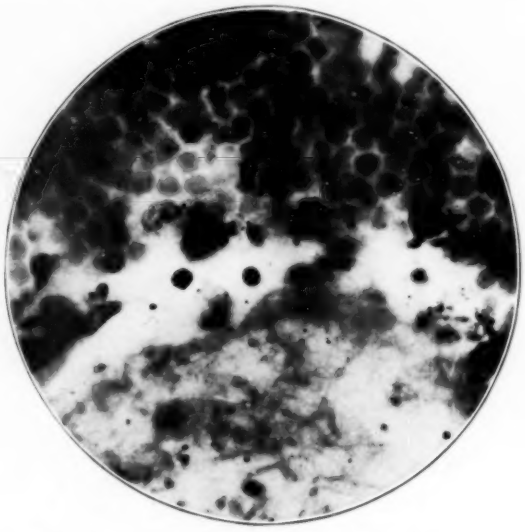


Fig. 11.—Vessel wall necrosis in gunshot wound. Hematoxylin-eosin stain; × 720.

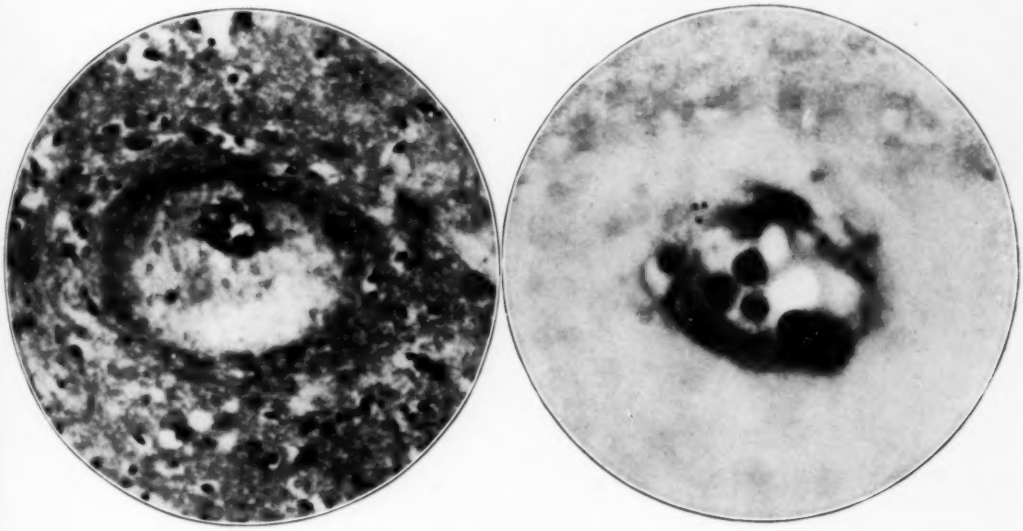
the opinion that such changes may also be due to arterial spasm; after the angiospasm has passed, the blood flows back into the pathologically changed vessels, and diapedesis takes place. Kinetic disturbances of this kind may occur in arteries under high arterial pressure (fig. 4).

Boehne [7] always found serious arteriosclerosis, but he insisted on the primary nature of the disease of the brain tissue, saying that the vascular walls are only secondarily affected. He could not accept the theory of an isolated spasm of intracerebral vessels, because physiology

7. Boehne: Beitrag zum Problem der apoplektischen Hirnblutung, Beitr. z. path. Anat. u. z. allg. Path. **78**:260 (Sept. 5) 1927.

teaches that one has always to do with entire vascular areas, which contract or dilate under sympathetic or parasympathetic influence. He believed that the ischemia has a mechanical cause: (1) in the case of arteriosclerotic changes of intracerebral and extracerebral vessels; (2) through spasm of extra cerebral arteries of the base and pia. There are two forms of hemorrhages: (1) extravasation of erythrocytes into the perivascular sheaths and nearby cerebral tissue, and (2) large hemorrhages.

There is no complete angiosclerosis, but the tissue balance, according to Weigert, is disturbed. There is a high arterial pressure, and there is no normal pressure of the tissue to counteract it; in that way diapedesis



A B

Fig. 12.—*A*, vessel wall degeneration in hemorrhage in gunshot wound. Hematoxlin-eosin stain; × 200; *B*, high power of *A*. Hematoxylin-eosin stain; × 720.

takes place through the changed, although not necrotic, vascular wall. In the veins, in which there is no question of high pressure, one finds the stasis as a contributory causative factor. The large hemorrhage can be caused only by the rupture of a large branch (fig. 5).

DeVries [8] assumed that arteriosclerosis causes such a marked constriction of certain vessels that both cerebral tissue and vessels undergo necrosis through ischemia in the area of those vessels. The little blood that still flows through the narrow parts leaves the altered vessels by diapedesis (fig. 6).

8. de Vries, W. M.: Over Apoplexia cerebri, Nederl. tijdschr. v. Geneesk. **72**:650, 1928.

According to Rühl,[9] every hemorrhage is preceded by a severe atheromatous ulcer formation of a local nature. This ulcer corrodes so deeply and the wall of the blood vessel is locally so weakened that at last it cannot resist the blood pressure in the vessel and bursts (fig. 1). Rühl gives the following arguments for this conception: In every case of cerebral hemorrhage, more severely atheromatous vessels are found in the cerebrum than in any other organ. In the cerebrum the vessels are already weaker than in other organs because of the absence of an elastic muscular longitudinal layer. An increased blood pressure raises the possibility of hemorrhage. It is well known that considerably fewer hemorrhages occur in the cortex than in the brain stem. Accordingly,

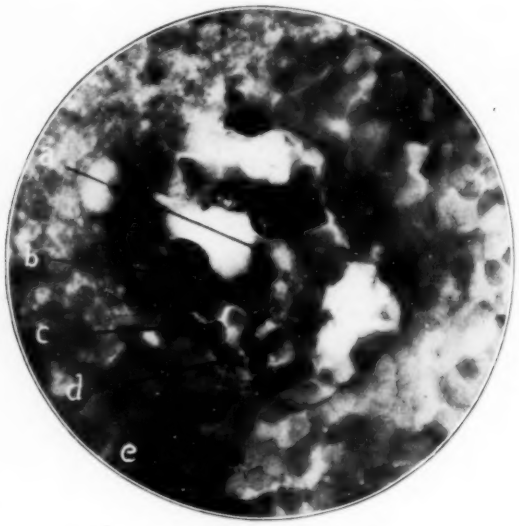


Fig. 13.—Blood inside and outside the meso-ectoderm membrane in gunshot wound; *a*, blood corpuscles in the vessel lumen; *b*, vessel wall; *c*, blood corpuscles in the perivascular space of Virchow-Robin; *d*, meso-ectoderm membrane; *e*, blood corpuscles in the glia chambers of Held. Hematoxylin-eosin stain; × 720.

Rühl found the vessels of the stem more often and more severely altered arteriosclerotically than those of the cortex. Moreover, he was able to point to the greater abundance of vascular anastomoses in the cortex, through which eventual pressure differences in the cortex could be more rapidly equalized than in the stem. When the hemorrhage has begun by a rupture in a severely atheromatous vessel, as has already been described, the outflowing blood has, according to Rühl, such destructive

9. Rühl: Arteriosklerotische Gefässruptur oder Spasmus als Ursache der apoplektischen Gehirnblutung, Beitr. z. path. Anat. u. z. allg. Path. **78**:160, 1927.

power that small blood vessels in the periphery are ruptured. These small vessels in their turn cause hemorrhages and increase the total amount of hemorrhage. Other vessels are so greatly stretched that blood passes through their walls by diapedesis.

Staemmler [10] questioned whether a change of cerebral substance and of the vessels precedes a hemorrhage. He investigated cases of traumatic encephalomalacia, especially cases of bullet wounds. Comparing eleven cases of trauma and four cases of encephalomalacia, he found that they were identical in all respects. He assumed especial fermentative processes in the brain and was of the opinion that great quantities of autolytic ferments are formed. A remarkable feature was the early

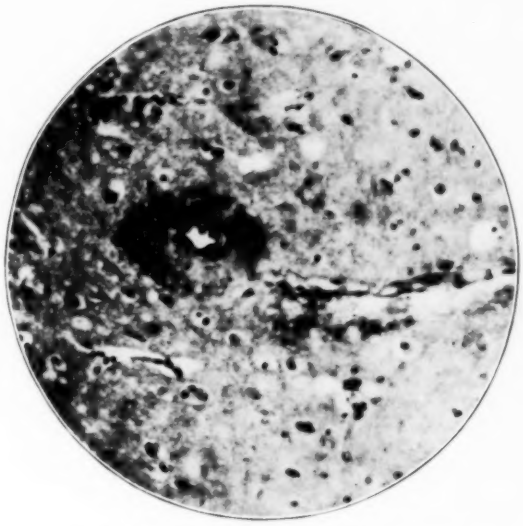


Fig. 14.—Propagation of blood along a vessel in gunshot wound. Hematoxylin-eosin stain; × 160.

occurrence of vascular changes. The necrobiotic process had proceeded from without toward the center, i. e., from the more resistant fibrous tissue to the endothelium, from which he concluded that ferments played a causative part.

PERSONAL OBSERVATIONS

My investigations are based on cases of apoplexy in older and younger persons, and on cases of gunshot wounds, in which the patients lived for several hours. I found large hemorrhages from rupture of large vessels the rule. There, of course, a disharmony existed between

10. Staemmler: Ueber Veränderungen der kleineren Hirngefässe in apoplektischen und traumatischen Erweichungsherden, Beitr. z. path. Anat. u. z. allg. Path. **78**:408, 1927.

the blood pressure in the vessel at the moment of rupture on the one side and a weakness of the vessel wall on the other. In the cases in which weakness of the vessel wall plays the chief part, the ruptured vessel will generally not be the only one with a weakness of the wall, but in the adjacent area other vessels with the same alteration of the wall will be found.

To illustrate I will describe some cases of hemorrhages that I examined:

REPORT OF CASES

Case 1.—A pontile hemorrhage occurred in a young woman. The great force here developed is evident from the breaking through into the ventricles. When I

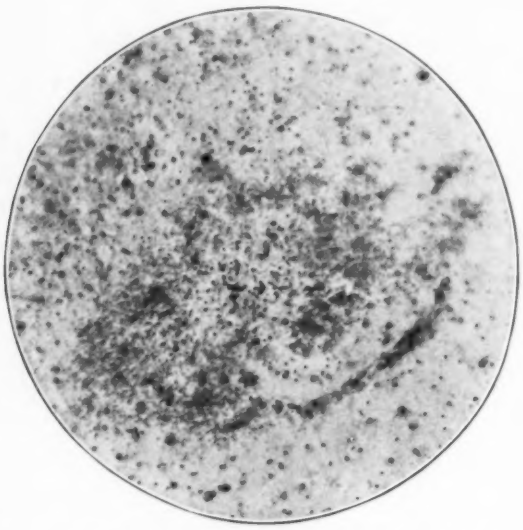


Fig. 15.—Circular hemorrhage. Hematoxylin-eosin stain; × 100.

examined the vessels near the large hemorrhage, I found many of them altered and some ruptured; an eventual arteriosclerosis works in this direction. Figure 7 shows a vessel from the area near the large hemorrhage; the vessel itself is obviously altered, and the blood is streaming out of the vessel. The more or less degenerated vessels in the adjacent area could have been degenerated before the hemorrhage, in the same way as the large vessel was degenerated before the rupture, or after the hemorrhage, viz., as a consequence of mechanical or chemical influences.

Case 2.—In a hemorrhage in an old man I found the development of an aneurysma dissecans. Figure 8 gives an instructive instance of blood in the perivascular space of Virchow-Robin. Confirmation of the conception that the blood passes into the perivascular spaces is found in figure 9, which shows that the blood has made its way into the glia spaces of Held. This takes place even along the thinnest branches of the vessels. The blood seems to spread through the perivascular spaces.

Normal as well as altered vessels are found in the area of a hemorrhage; it can be demonstrated rather easily that in many arterioles there is no necrosis. By examination of the anatomic structure, one finds that the intima and media are normal. The wall elements in the center of the focus are normally stained. Many of these normal vessels are found ruptured. When no alteration of the vessel wall can be demonstrated, one must consider the possibility of secondarily ruptured vessels as a consequence of the blood mass, which forces its way and pushes everything aside. The blood coming from these small normal vessels and that which flows out of the degenerated vessels will greatly increase the quantity of the extravasated blood.

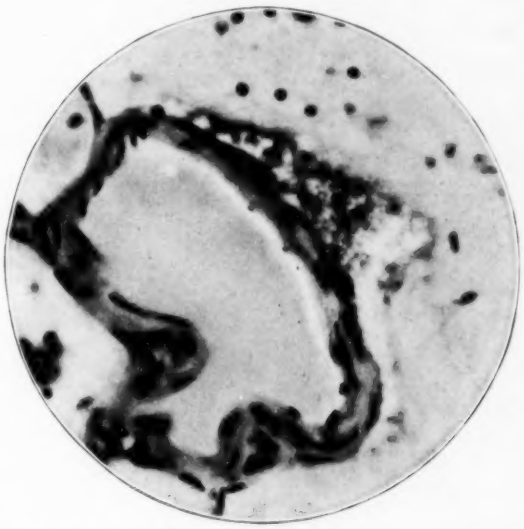


Fig. 16.—Coagulation beside a vessel wall. Hematoxylin-eosin stain; × 400.

If the hemorrhage lasts longer, several factors have an influence. There may be ischemia and chemical action from the changed tissue or from the extravasated blood. Tissue reaction develops, especially along the vessels; a perivascular tissue cell infiltration arises (fig. 10).

COMPARISON WITH GUNSHOT WOUNDS

Comparing the observations in several cases of apoplexy with those made in a study of gunshot wounds, one finds that there are curious analogies between them. In a relatively short time, vessel walls with necrosis are visible in the circular space of the destruction by a gunshot wound (fig. 11). It is striking that the necrobiotic process of the vessel wall is progressing from the outside to the inside. Properly

speaking, it also has begun in a tissue that according to its connective tissue structure ought to have more resistance. Therefore here one must think of chemical influences of the surroundings, as pointed out by Staemmler. A typical instance of the vessel-wall degeneration is shown in figures 12 *A* and *B*.

It could be demonstrated that there was blood inside and outside the meso-ectoderm membrane; the blood corpuscles were lying in the perivascular space of Virchow-Robin, and there was transportation of blood through the glia spaces of Held (figs. 13 and 14).

Near a gunshot wound there is also necrosis of vessels, in consequence of influences originating in the surroundings. The extravasated

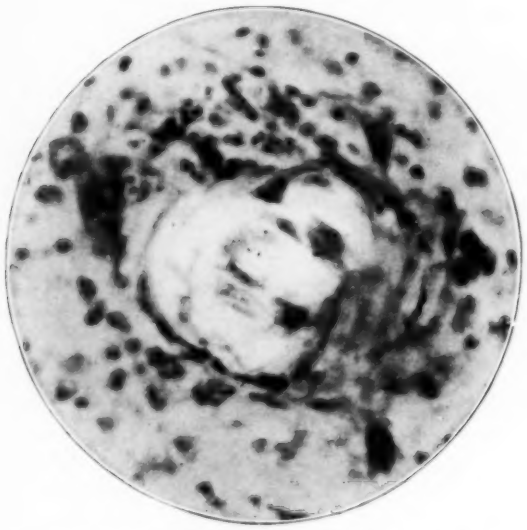


Fig. 17.—Tissue cell (Gewebigzellige) infiltration. Nissl stain; × 400.

blood propagates through the perivascular spaces of Virchow-Robin and through the glia spaces of Held, as I found in apoplexia cerebri. Thus in both apoplexia cerebri and gunshot wounds there are mechanical and chemical influences that are of great importance.

According to Ricker and de Vries, a circular hemorrhage is formed if blood from the surrounding vessels enters the diseased vessel area. Figure 15 shows an instance of a circular hemorrhage, which I have often found in my cases. It is characterized by a particular hyaline center and coagulation necrosis, often with a hyalinized, necrotically shut-off capillary or precapillary. Around this area there lies a zone of hemorrhage, which is mostly circular, sometimes occurring only in sectors and often only a small necrosis (Rühl). The cause of the necro-

biotic process must be attributed to the mechanical or chemical processes already mentioned.

In a case that clinically was first thought to be one of softening due to thrombosis, autopsy revealed a hemorrhage; microscopically, however, it appeared that there were both hemorrhage and softening. This, then, was a case of red softening. It is interesting to see that here there were special alterations, uncommon in ordinary hemorrhages. There were found: erythrocytes and scavenger cells, also erythrocytes in scavenger cells, coagulation beside a vessel wall (fig. 16) and tissue cell (Gewebigzellige) infiltration (fig. 17). Here also were the symptoms of a secondary inflammatory process after the degeneration and

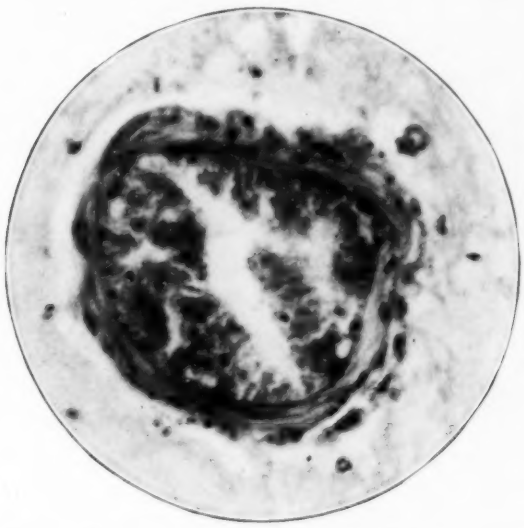


Fig. 18.—Arteriole in the center of a pale territory. Hematoxylin-eosin stain; × 244.

the necrotic alterations of the vessels. The wall of the hemorrhage displayed three distinct layers, not unlike the wall of an abscess: The innermost layer was brain tissue mixed with extravasated material, the middle layer new-formed vessels with glia and lymphocytic elements and the outermost layer gliosis. There was thus an attempt to shut off the process.

Hemorrhages in poliencephalitis hemorrhagica superior are occasionally top shaped. There are arterioles in the necrobiotic focus with walls altered as seen in figures 18 and 19. This is again according to my conception that the pressure of the extravasated blood will cause anemia and, in consequence, degeneration of the vessels.

SOME CLINICAL COMMENTS

Westphal has drawn attention to the premonitory symptoms that precede apoplexy: headaches, vertigo, fatigue, depression and anxiety, as well as difficulty in thinking and tendency to vomit and yawn, which are also found in hypertension. Therefore it is of the greatest importance that the physician inquire minutely into the anamnesis of the patients in order to learn what preceded the attack. In cases described by Globus and Strauss [11] the patients were not ill beforehand, although there were definite characteristic anatomic lesions showing diffuse degenerative vessel disease, which had existed for a long time.

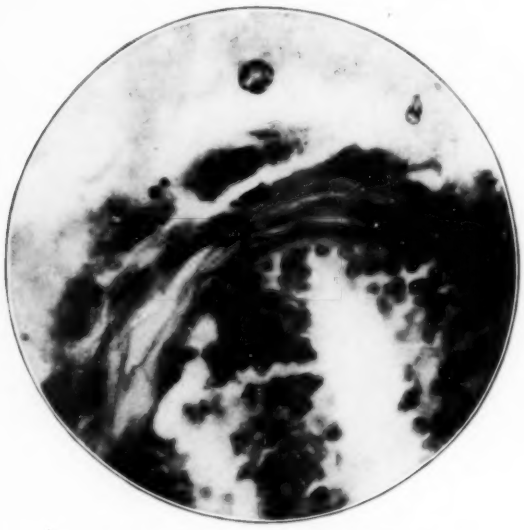


Fig. 19.—Arteriole wall in pale territory. Hematoxylin-eosin stain; × 594.

In the second place, there are cases in which there is some clinical indication of a preexisting disease of the brain without symptoms of a focal destructive disease.

Important also are the investigations of Spielmeyer,[12] who demonstrated that local circulatory disturbances, not resting on material lumen and vessel alterations, may cause cerebral tissue destructions, there being histologically intact vessels in the territory of necrosis. The lesions may be merely a slight ischemic change in the nerve cells, causing them

11. Globus, J. H., and Strauss, I.: Massive Cerebral Hemorrhage, Arch. Neurol. & Psychiat. **18**:215 (Aug.) 1927.

12. Spielmeyer: Vasomotorisch trophische Veränderungen bei zerebraler Arteriosklerose, Monatschr. f. Psychiat. u. Neurol. **68**:605, 1928.

to take the Nissl stain poorly; under low power magnification, the specimens show pale areas. In one case the patient was stuporous for three days before he died. In another case the patient was comatose, with paraphasia and left hemiparesis for four weeks before death; in this case foci were found in the right central gyrus. It is true that it is often difficult to say that the pale areas are due to ischemia and are not artefacts; skilful staining by the original Nissl method is the best criterion.

It is not uncommon to make the clinical diagnosis of a cerebral hemorrhage and then to have the pathologist find no gross lesion at autopsy. Such cases used to be spoken of as "hemiplegia without anatomic observations," but Spielmeyer's observations have demonstrated that although in such cases there is no obvious lesion, careful histologic examination will show widespread and characteristic ischemic lesions. He has found these lesions in the brains of patients who lived for only six hours after the onset of symptoms. Gildea and Cobb [13] have been able to produce similar lesions in the brains of cats by impeding the cerebral circulation for only six or eight minutes.

It is thus possible to explain on a basis of transitory anemia the various evanescent hemiplegias, monopareses and aphasias that are so commonly met with in clinical practice; total recovery may take place in one case, and in another that appears no worse at the beginning the neurologic signs may become permanent disabilities. In the first case there is evidently only a passing cerebral anemia, not prolonged enough to cause tissue destruction, and in the second there is actual tissue destruction in the cerebrum. Just how long certain brain cells can stand a given grade of anemia is still unknown; much more research must be made and new methods must be devised before these problems are solved. Spielmeyer's pathologic studies, however, indicate that many vascular disturbances, in young patients especially, may be due to vasomotor spasm in the brain. The physiologic experiments of Forbes and his co-workers [14] prove that the cerebral blood supply may be influenced by vasomotor control of the intracranial arteries and veins. So the problem of cerebral hemorrhage is still new and challenging to investigators.

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13. Gildea, E. F., and Cobb, Stanley: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

14. Forbes, H. S., and Wolff, H. G.: Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928. Cobb, S.: Relationship of Cervical Sympathetic Nerves to Cerebral Blood Supply, Am. J. M. Sc. **178**:528, 1929.

SUMMARY AND CONCLUSIONS

One may distinguish between the hemorrhage from a large vessel and hemorrhages from the small vessels in the adjacent area: 1. The large hemorrhage is caused by the rupture of a vessel and is dependent on an atheromatous ulcer formation of local nature which bursts, according to the conception of Rühl, with outflowing blood forcing its way into the tissue and causing mechanical injury. 2. Small vessels in the adjacent area with altered walls and also small vessels without alteration may thus be caused to rupture. 3. In addition, there is ischemia in some parts of the environment with consequent necrosis of the vessel walls and of the brain tissue; moreover, there are the chemical influences of the extravasated blood in the tissue; so vessels that are secondarily altered also rupture.

The pathway of the blood could be demonstrated; it goes along the perivascular spaces of Virchow-Robin or along the perivascular glia chambers of Held. These two forms of secondary hemorrhages contribute to the quantity of extravasated blood.

The study of gunshot wounds showed alterations analogous to those in apoplexia cerebri, dependent on the same principles. The tissue bordering on the gunshot wound showed necrobiotic processes of the walls of the small vessels and blood in the perivascular spaces. Thus acute lesions are shown to have vascular wall degenerations.

In the cases of a circular hemorrhage and of poliencephalitis hemorrhagica superior there also was found a necrobiotic process of the small vessels, dependent on mechanical and chemical influences.

In "red softening," tissue cell infiltration was found, with degeneration and alteration of the vessels; this could be demonstrated in both recent and old hemorrhages. Besides, it was found in the red softening that the wall of the hemorrhage consisted of three distinct layers from the inside to the outside, (1) brain tissue with extravasated material, (2) new-formed vessels with glia and lymphocytic elements and (3) gliosis.

In connection with several cases of cerebral hemorrhage in young patients and the so-called "hemiplegia without anatomic observations," one is compelled to postulate a vasomotor disturbance rather than one of the processes already described.

THE CEREBRAL CIRCULATION

XIII. THE QUESTION OF "END-ARTERIES" OF THE BRAIN AND THE MECHANISM OF INFARCTION *

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Cohnheim [1] in his monograph on embolic processes, published in 1872, first clearly enunciated the theory that infarcts could occur only where there was no anastomosis between arteries. In his own words: "Alles nämlich hängt davon ab, ob hinter dem Pfropf, zwischen ihm und dem betreffenden Capillargebiet, noch ein arterieller Zweig abgeht, der mit einer anderen beliebigen Arterie in unmittelbarer Continuität steht, also eine echte Collaterale oder richtiger gesagt, Anastomose bildet, oder ob eine solche fehlt." He thus impressed the medical world with the idea that unless "end-arteries" supplied an organ, or part of an organ, no infarction could occur. He made little reference to the brain, but in one place said that emboli in the brain usually cause simple necrosis, while in the spleen and lung the infarcts are usually hemorrhagic ("hämoptoische").

In spite of anatomic studies which have clearly shown the presence of anastomosis between the different arteries and arterioles of the brain, this idea of "end-arteries" has persisted and has been handed down from textbook to textbook. Most books on cerebral anatomy say that the arteries entering the brain at once become terminal end-arteries, each vessel becoming the sole contributor to the region supplied by it, and that there is no anastomosis between the smaller arteries of the brain. Some authors even state that in the cerebral cortex a capillary plexus is confined to the territory of the artery from which it arises and does not connect with any adjacent capillary plexus.

The most convincing recent work on the anatomy of the cerebral vessels is that of Temple Fay [2] on the larger arteries of the brain, and

* Submitted for publication, Sept. 25, 1930.

* Read at a Meeting of the Boston Society of Psychiatry and Neurology, Jan. 16, 1930.

* From the Department of Neuropathology, Harvard Medical School.

1. Cohnheim, J.: Untersuchungen über die embolischen Processe, Berlin, A. Hirschwald, 1872.

2. Fay, Temple: The Cerebral Vasculature: Preliminary Report of Study by Means of Roentgen Ray, J. A. M. A. **84**:1727 (June 6) 1925.

that of Lorente de Nò [3] and Pfeifer [4] on the small arteries, venules and capillaries. Fay made injections of metallic mercury into human brains removed at autopsy and then made records of the injection by means of stereoscopic x-ray plates. The results are clearcut and the illustrations in his paper prove that there are many well defined anastomotic arterial trunks between the anterior, middle and posterior cerebral arteries. There is also anastomosis between the arteries of the right and left hemispheres. He believed that there is no evidence of anastomosis between the large vessels supplying the subcortical white matter nor in the vessels of the basal ganglia. He stated that there is evidence of definite end-arteries in the cortex, but did not explain what this evidence is. He thought that his studies indicate that communications are numerous between the various different zones of the vascular supply of the brain, and that these communications are of considerable size and are available for collateral circulation. He believed, however, that "cortical end-arteries do exist to a large extent."

Pfeifer, in two beautifully illustrated monographs, proved beyond doubt that there are no end-arteries in the brain. He showed by his injection preparations that the capillary bed of the whole cortex is one endless network ("endloses Kontinuum"), and stated that a red blood cell if given motive power could travel through normal, open vessels from the occipital pole to the tip of the frontal lobe. Moreover, there is much anastomosis between the different arterioles and between the different venules. In the pia-arachnoid it is not uncommon to find an arteriole opening into a venule.

In 1925 and 1926, I carried out some studies on the anatomy and physiology of the cerebral capillary circulation.[5] Many preparations were made of rabbit brains by injecting "Berlin blue" solution into the arteries of the living animals at a pressure of from 200 to 225 mm. of mercury. Sections of the brains were cut 200 microns thick and cleared without staining. A study of such a preparation with a binocular microscope allows the observer to follow any given vessel for a long distance; by this method I was able to satisfy myself that the capillary bed of the cortex and of the basal ganglia was a continuous network. Arteries entered this rich bed of the cortex largely from the pia, but a few came up from the region of the basal ganglia to supply the deep

3. Lorente de Nò, R.: Ein Beitrag zur Kenntnis der Gefässverteilung in der Hirnrinde, J. f. Psychol. u. Neurol. **35**:19, 1927-1928.

4. Pfeifer, R. A.: Die Angioarchitektonik der Grosshirnrinde, Berlin, Julius Springer, 1928; Grundlegende Untersuchungen für die Angioarchitektonik des menschlichen Gehirns, Berlin, Julius Springer, 1930.

5. Cobb, S., and Talbott, J. H.: Studies in Cerebral Circulation: II. A Quantitative Study of Cerebral Capillaries, Tr. A. Am. Physicians **42**:255, 1927.

white matter and joined the capillary bed from below. Such a study convinces one that in the rabbit there are no end-arteries in the brain (fig. 1).

Of course, preparations like these cannot be made of human brains, for intravital injection is essential if all the fine vessels are to be com-

Fig. 1.—Capillary network in a thick section of cortex (200 microns, area temporalis inferior of rabbit). The blood vessels were injected with Berlin blue in vivo; the brain was fixed, cut and cleared without staining. The photograph shows the larger radial vessels plunging in from the pia (arterioles and venules) and the rich capillary anastomosis, especially in the richly cellular middle laminae. The outer five laminae of the gray matter are shown; × 106.

pletely filled. By using a stain, however, that makes erythrocytes appear black and leaves the rest of the tissue essentially unstained,[6] interesting

6. Morgan, L. O.: Iron Hematoxylin as a Myelin-Sheath Stain and Neutral Red Ripened by Colon Bacillus as a Nerve-Cell Stain, Anat. Rec. **32**:4, 1926.

observations may be made on human material. One infant that died of asphyxia at birth had a greatly congested cortex, and preparations from this brain showed a capillary network just as continuous and just as rich as that seen in the cats and rabbits (fig. 2). The filling with red cells is not as complete as the mechanical filling of injected specimens and some parts of this human brain are not as congested as others, but the similarity of the anatomy to that seen in rabbits and cats indicates that in the human brain there is an endless net of arterioles, capillaries and venules throughout the cortex and other similar networks in the ganglia of the base and brain stem. The recent work of Pfeifer [7] on human material corroborates this.

I have now presented evidence to show that there are no end-arteries in the brain. The old theory that the brain is supplied by end-arteries appears to be based entirely on the conventional idea that an infarct occurs only when the blood supply is entirely shut off and that in order to produce this infarct there must be end-arteries. It is well known that infarcts occur in the brain. This means that Cohnheim's theory—that end-arteries are a prerequisite for the formation of embolic infarcts—is wrong. This becomes obvious if one considers the other organs of the body, for in a tremendously vascular organ such as the spleen, where there is an "open circulation," [8] infarcts occur frequently; so, too, in the heart muscle, shown by Wearn [9] to have one of the richest capillary beds of any organ.

Cohnheim does not seem to have made any statement about anastomosis between different areas of the capillary bed; he seems to have regarded end-arteries as those which supplied part of a tissue and had no arterial connection with any other artery. Connections between the finer branches (arterioles and capillaries) were apparently not considered important by him. Later writers, however, have specifically stated in textbooks that the capillary bed of one end-artery was distinct and separate from that of another. My observations on the brain lead me to controvert this flatly, and to agree with Pfeifer that the capillary bed is an endless continuous net, spreading over large portions of the brain, supplied by many different arteries. There is also evidence that points strongly to this being the fact in most organs of the body. In general, the greatest anastomosis is in the capillary bed; there is much anastomosis between arterioles, and a definite but lesser amount between arterial trunks of larger size.

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7. Pfeifer (footnote 4, first reference).

8. Robinson, W. L.: The Venous Drainage of the Cat Spleen, Am. J. Path. **6**:19, 1930.

9. Wearn, J. T.: J. Clin. Investigation **1**:572, 1924-1925.

Fig. 2.—Photomicrograph of gray matter from a human brain showing the rich capillary supply. This illustration may be compared with figure 1 but it is to be remembered that figure 1 is made from a section that is 200 microns thick, while this was cut at 20 microns. Therefore the capillary network is only observed in one thin plane, and there are no loops and few anastomoses visible. Capillary counts made on this specimen show that there are about 50 microns of capillary length per one hundred thousand cubic microns of brain. This indicates that the vascularity of the brain of the rabbit is similar to that of man. (Morgan's stain.)

A diagrammatic sketch of the circulation of the brain has been made to explain this (fig. 3). An obstruction at *O* would undoubtedly greatly decrease the oxygen supply to the gray matter near *G*, but this would be temporary because the arterial blood from *A'* and *A* would reach that tissue through the connecting arterioles and capillaries. Venous blood (from *V*) would also come in, to a certain extent, through the capillary

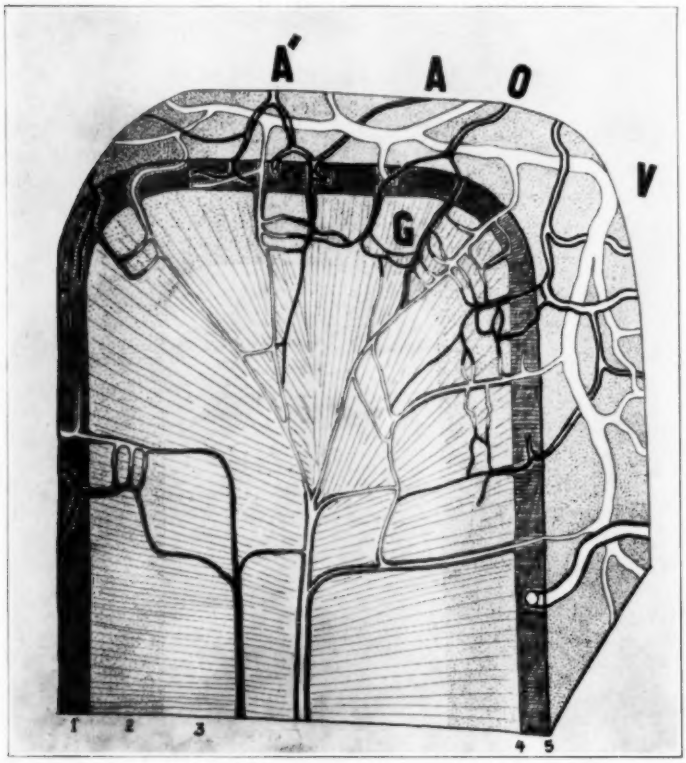

Fig. 3.—Diagram of the circulation of a gyrus of the brain. *1* indicates subarachnoid space; *2*, gray matter; *3*, white matter; *4*, pia; *5*, arachnoid membrane.

bed, but at a very low pressure and bearing little oxygen. If these auxiliary supplies of oxygen proved inadequate to meet the needs of the cells, the vessel walls would be weakened and dilated, and edema and extravasation of erythrocytes would take place. This would tend to shut off what little oxygen supply there was left, and the "red infarct" would become a "pale infarct" with necrosis. It is, however, not a question of anemia; plenty of blood remains in the infarcted area; in fact,

congestion is one of the first reactions. Professor Greenfield,[10] of Edinburgh, taught years ago that even in the kidney and spleen all infarcts begin by being red or hemorrhagic and that the pale or anemic infarcts are really a later stage of the red ones. In a long series of experiments, many of them conducted under the direction of Greenfield, it was proved by direct observation that, following ligature and embolus, the earliest changes are areas of purplish congestion. They appear a few hours after obstruction to the arterial supply to part of the kidney. At the end of about twenty-four hours such an area has become pink and is surrounded by a pale boundary layer. At about forty-eight hours the surface may still be more or less pink, but deep in the middle of the infarct is a pale region, not swollen but sunken after cutting. Microscopically, these early infarcts show the capillaries engorged with blood and the parenchymatous cells undergoing necrotic changes. In the last stages the whole infarct is pale and shows advanced necrotic change.

The explanation of this congestion in an infarct, according to Cohnheim, was that there was a reflux of blood through the veins and capillaries into the infarcted area, but the experiments of Greenfield and his co-workers proved that this was not true; they concluded that the marked hyperemia is due to collateral arterial blood supply. This collateral supply is often unable to maintain the outflow through the veins and as a result thrombosis may occur in the veins. This increases the engorgement.

When there is oxygen-lack in any tissue, chemical changes immediately take place. In the brain the result is edema, dilatation of blood vessels,[11] diapedesis of red cells and necrosis. All this occurs quickly at the center of the anoxemic area. At the edge of this area is a belt of less marked chemical change, and this merges into the normal tissue around it. The ganglion cells of the brain are known to withstand even partial anoxemia poorly; from five to ten minutes of greatly reduced blood supply will cause necrosis of these cells.[12] Moreover, the rich capillary bed in the cell layers in the cortex [13] and the bright red arteries

10. Greenfield, W. S., quoted by Beattie, J. M., and Dickson, W. E. C.: Textbook of Pathology, St. Louis, C. V. Mosby Company, 1926, p. 156.

11. Wolff, H. G., and Lennox, W. G.: Cerebral Circulation: XII. The Effect on Pial Vessels of Variations in the Oxygen and Carbon Dioxide Content of the Blood, Arch. Neurol. & Psychiat. **23**:1097 (June) 1930.

12. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

13. Cobb, S.: The Cerebral Circulation: VIII. A Quantitative Study of the Capillaries in the Hippocampus, Arch. Surg. **18**:1200 (April) 1929.

and blue veins seen in the living cerebral circulation [14] indicate a rapid metabolism and great dependence on oxygen supply. Relative lack of oxygen is therefore all that is needed to start the train of events that leads to an infarct, and what is called "ischemic" or "anemic" necrosis.

If, then, one defines "end-arteries" as those arterial branches which in no way connect, even through the capillary bed, with other arterial branches, there are probably no end-arteries in the body, certainly not in the brain. If the definition is that the branch in question must have no connection with other arterial branches (including arterioles) there probably are no end-arteries except perhaps a few in the kidney, spleen, mesentery and retina. My observations on the brain would lead me to believe that there are none there, even in the basal ganglia. If one considers any artery that does not have obvious anastomosis of branches large enough to be called truly arterial to be an "end-artery," one may find many such in the organs enumerated, and a few in the brain. Functionally speaking, however, the capillary and arteriolar anastomoses keep the arterial tree from acting as the sole blood supply of any part.

The edema is probably the most effective factor in shutting off blood from anastomosing capillaries and other small vessels, for these have a low blood pressure, and the swelling quickly blocks the flow as in wheal formation in the skin. Thus, in the brain, occlusion of an artery in spite of arterial and capillary anastomosis can cause enough reduction of oxygen supply to produce necrosis. It is a matter of relative anoxemia (not of anatomically perfect anemia) in a tissue more dependent on its oxygen supply than any other tissue in the body.

14. Forbes, H. S.: The Cerebral Circulation: I. Observation and Measurement of Pial Vessels, Arch. Neurol. & Psychiat. **19**:751 (May) 1928.

ORIGIN AND DEVELOPMENT OF GIANT CELLS IN GLIOMAS *

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The study of gliomatous tumors has been considerably advanced in recent years by the development and perfection of neuroglial staining methods. The credit for this should be given to the Spanish school of neurohistologists, notably Cajal and del Rio-Hortega. The methods of using gold and silver solutions of the former and the technic of silver carbonate staining with all its variations of the latter have brought to light many details of importance in the furtherance of knowledge of the structure of the neuroglia. To Cajal and his school is due much of the present knowledge of the histogenesis and structure of the astrocytic neuroglia, while del Rio-Hortega has demonstrated clearly the histogenesis, morphology and pathologic variations not only of the oligodendroglia, but also of the other constituent of the third element, the microglia or mesoglia. These studies have clarified remarkably the knowledge of the normal structure of the neuroglia and mesoglia. In so doing they have made clearer the nature of gliomas. Since it has long been recognized that these tumors arise from the neuroglial elements in the brain, it remained merely for a clarification of these elements to make certain the knowledge of the structure of gliomas.

Bailey and Cushing,[1] in 1926, made a tremendous stride forward in the understanding of gliomas, in both their histologic and their clinical relationships, by the application of the newer methods and knowledge in relation to the neuroglia. Their monograph afforded the first sufficiently satisfactory classification of the gliomatous group of tumors, and pointed the way to a further understanding of these neoplasms.

GLIOMAS WITH A PREPONDERANCE OF GIANT CELLS

Certain types of cell groups in the gliomas remain obscure in their significance. Among these are the giant cells that are found in large

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* From the Laboratory of Experimental Histopathology in the Instituto Nacional of Oncologia, Madrid, and the Surgical Wards and Neuro-Surgical Laboratory of the University Hospital, Philadelphia.

1. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group on a Histogenetic Basis, Philadelphia, J. B. Lippincott Company, 1926.

numbers in some gliomas. Bailey and Cushing mentioned their presence chiefly in the spongioblastoma multiforme group, in which they appear to be most frequently seen and most numerous. Some gliomas, however, are made up largely of giant cells, so much so that Stroebe [2] grouped some tumors of neuroglial origin under the name "Riesenzell-gliome." Borst [3] described a tumor of this nature, and Ribbert [4] mentioned the numerous giant cells in a type of tumor which he accepted as a giant cell tumor. These cases would now be classified as spongioblastomas.

Achucarro [5] described two gliomas consisting largely of giant cells. It is impossible to state the exact nature of these tumors, since the tannin-silver method of Achucarro is unsatisfactory for demonstrating the exact nature of the cellular structure. One of the tumors, that Achucarro described as being constituted almost exclusively of estrellated giant cells was located in the cerebrum. The other tumor, found in the pons, also contained numerous giant cells but very few neuroglia fibers. The tumor cells were chiefly estrellated, with long prolongations, among which were true astrocytes. These stellar-shaped giant cells contained many nuclei situated peripherally, not rarely forming a crown effect, and often with the nuclei united by fine filaments. Many of the smaller cells in the tumor were multinucleated and were less rich in protoplasm than the larger ones. Cellular divison was almost exclusively amitotic, but occasionally there was found among the giant cells a nucleus in mitosis. From the description given by Achucarro it would appear that the tumor was a spongio-astroblastic type of glioma, made up almost entirely of estrellated giant cells, among which were numerous astrocytes.

Rio-Hortega [6] recently described a giant cell glioma which presented itself subcutaneously at the inner canthus of the eye of a child aged 4 months. Giant astrocytic neuroglia cells were numerous, especially in those portions of the tumor that adjoined the skin; they were characterized by the presence of many nuclei and poorly-staining, thick, flexuous cellular prolongations.

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2. Stroebe: Ueber Entstehung und Bau der Gehirnglioma, Beitr. z. path. Anat. u. z. allg. Path., 1885, vol. 18.

3. Borst, M.: Geschwülste des Rückenmarks, Ergebn. d. allg. Path. u. path. Anat., 1903.

4. Ribbert, H.: Geschwülstlehre, ed. 2, Bonn, F. Cohn, 1914.

5. Achucarro, N.: The Nuclei of Giant Cells in a Glioma, Trab. d. Lab. Cajal, 1910.

6. del Rio-Hortega, P.: Glioma subcutaneo de cellulas gigantes, Bol. de la Soc. espań. de biol. **12**:14, 1926.

GIANT CELLS IN OTHER GLIOMAS

Giant cells in greater or lesser numbers appear in various types of gliomas. They are frequently seen in gliomas with very slight differentiation of the cellular elements, as in the spongioblastomas and astroblastomas. They may occur also in more highly differentiated tumors, such as the astrocytomas, though they tend to be more numerous in the first-mentioned group. The differentiation between the two groups is definite and has been well described by Bailey and Cushing. The spongioblastoma multiforme group presents a picture different from that of the astroblastomas and astrocytomas. The multiform aspect of the cells, the presence of mitoses in many tumors, the degeneration, hemorrhage, and cysts and the varied protoplasmic structure of the cells tend to distinguish the spongioblastic tumor from the astroblastoma, which is composed of angulated cells in abundance, often attached to vessels and with rather loose structure. The differentiation is not so easy in spongioblastomas wherein the spongioblastic cells of a more or less primitive nature are far less numerous than the astroblasts. In these tumors containing giant cells it is not uncommon to find transitions between the astroblastic or astrocytic cells and the estrellated giant cells, which represent incomplete division of such cells. It is possible to follow the evolution of these giant cells from a uninuclear to a multinuclear development.

MATERIAL AND DESCRIPTION OF TUMOR

The material studied consisted of astroblastomas, astrocytomas and a spongio-astroblastoma involving the frontal lobe and penetrating into the corpus callosum. All the tumors contained giant cells, but the tumor of most interest in this connection was the last named; it contained many giant cells, and will therefore be described in detail. In the study of the finer structure of the giant cell nuclei, all the tumors mentioned were utilized.

The tumor concerning which details are given is described not as a giant cell tumor, but as a spongioblastoma in which giant cells were so numerous that an exceptional opportunity was offered to study the development of these large cells in a glioma.

The tumor consisted of a cortical portion and a callosal portion. In the callosum the tumor cells were numerous and closely packed; by proper staining they could be shown to consist largely of astroblastic and astrocytic elements. Giant cells in this portion were present but infrequent. In the cortex the tumor presented an appearance rich in cells, with numerous giant cells scattered throughout it (fig. 1). Many of the smaller cells, too, were multinucleated. These cells contained long, oval or pyriform nuclei closely packed together, but with no definite arrangement. Their chromatin was rather loosely packed in a granular arrangement, with a visible nucleolus in most cells. Many of these cells failed

to color intensely with specific silver carbonate stains for protoplasmic structure, indicating their embryonic character. The protoplasm in these primitive cells was scanty and delicate; it was either round or streamed out irregularly from the cells in very fine but short prolongations. The morphologic characters indicated that these cells were very young spongioblasts, some of which were differentiating into early astroblasts. Scattered among these cells were more mature cells which showed a decidedly greater avidity for silver. These cells were of

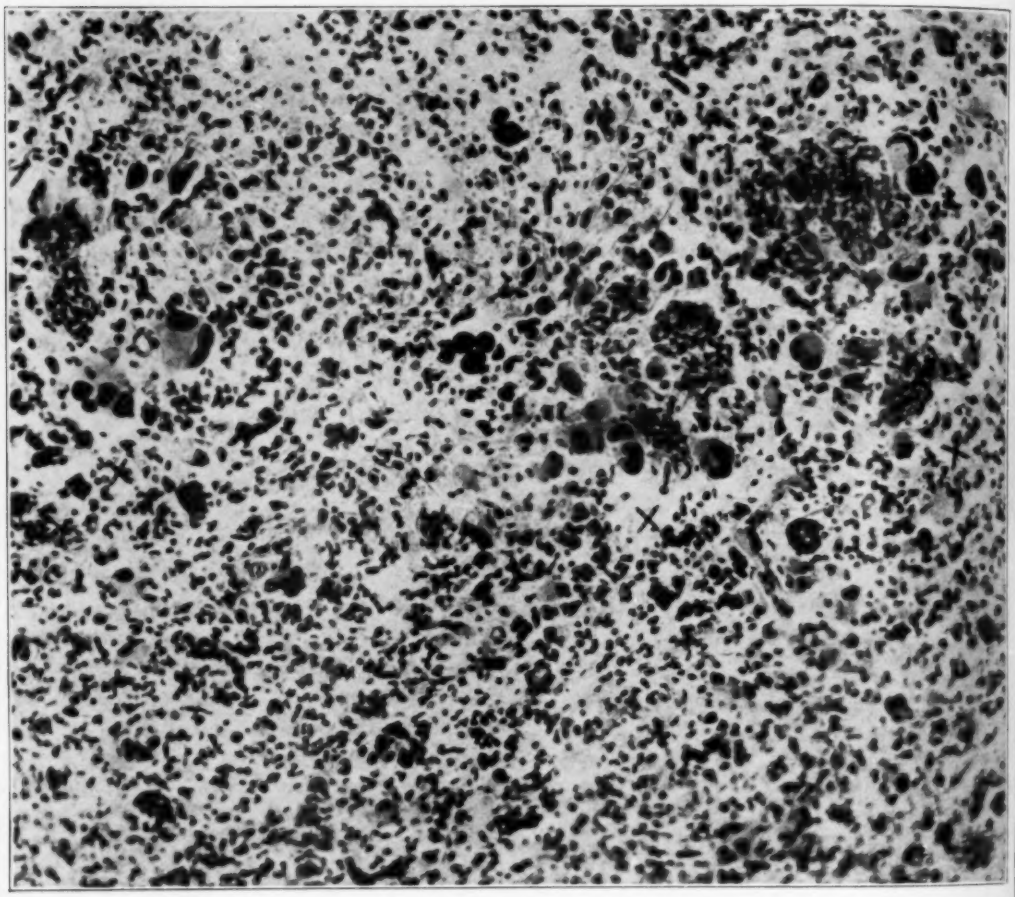

Fig. 1.—A low power view of the tumor showing the numerous giant cells. Silver carbonate method of del Rio-Hortega.

two types: smaller astroblasts, with irregular, angular bodies and short, fine prolongations, and large astrocytes in various stages of hypertrophy. Some of these were large, swollen, hypertrophied astrocytes, and others represented true monster cells.

That giant cells were numerous in the tumor can be seen in figure 1, at *X*, which indicates several foci of these cells. Scattered throughout the section many other giant cell elements are visible. It is possible from this to obtain an idea of

Fig. 2.—A field of giant cells. At *A* there are seen several nuclei some of which are connected by filaments. At *B* the numerous nuclei of a neoplastic giant cell are seen connected by filaments to a fairly well defined central point.

their relative frequency in the tumor. This field, taken from a typical portion of the tumor, shows numerous giant cells, arranged chiefly around a vessel. They are spread diffusely and thickly throughout the tumor, but are probably more numerous at the periphery of the tumor than in the center. Their relation to the vessels is definite, so that where the vessels are most plentiful the giant cells tend to be grouped and concentrated. Figure 2 shows a field of giant cells that are grouped around a large vessel. It gives some idea also of the frequency of the large and multinucleated elements. These perivascular giant cells are situated close to the wall of the vessel, some being attached to the vessel and others having no visible connection (figs. 3 and 4). Protoplasmic prolongations to the vessel wall are easily seen in many cases, as for example in figures 2*A* and 3*X*. All stages of development of these giant cells are seen around the vessels, from

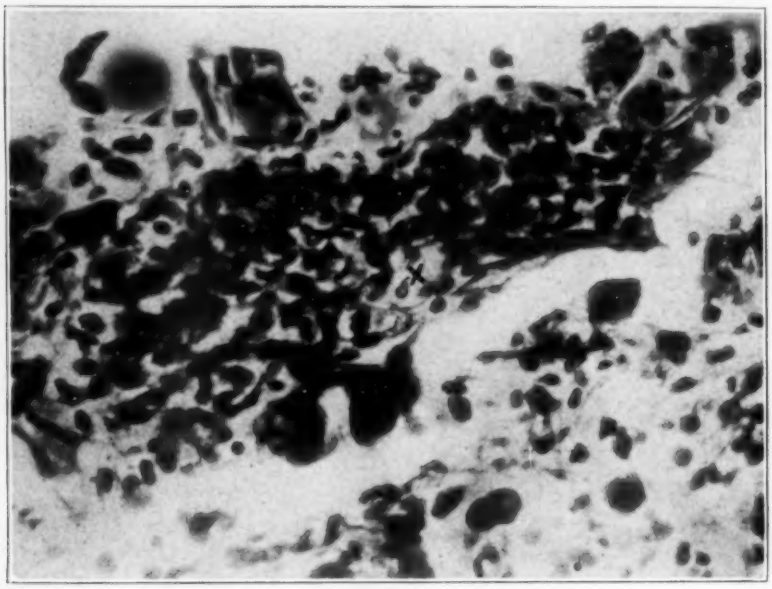

Fig. 3.—A number of giant cells gathered around a vessel. Silver carbonate method of del Rio-Hortega.

uninuclear to multinuclear development. The astrocytic nature of the cell is apparent close to the vessels. While in this region prolongations are easily visible, as one proceeds further away from the vessels the giant gliocytes assume a more rounded contour. Figure 4 shows a giant cell with a few of its prolongations staining visibly. In some cases a giant cell may be seen wrapped around a capillary[7] (fig. 5), maintaining a relationship exactly as in the case of the normal perivascular neuroglia described by Rio-Hortega.[8]

7. del Rio-Hortega, P.: Algunas observaciones acerca de la neuroglia perivascular cells of Andriezen. He first indicated clearly the special nature of these cells, and made clear their differentiation from the ordinary types of astrocytic neuroglia.

8. del Rio-Hortega, P.: Algunas observaciones acerca de la neuroglia perivascular, Biol. r. Soc. españ. de hist. nat., April, 1925.

Nerve fibers are abundant, as can be seen in figure 2. Relatively few fibers were destroyed by the glioma. Many fine axis cylinders are visible in the tumor, some containing nodular swellings and some being in the process of fragmentation. The presence of many relatively intact nerve fibers, however, is striking.

Neuroglia fibers are scattered diffusely through the tumor, intertwining among the cells. They are more abundant in the astroblastic and astrocytic portion of the tumor. Blepharoplasten are numerous. In the giant cells they are multiple, but in some uninuclear elements they are also numerous, indicating again the embryonic nature of the cells. The vascular supply of the tumor is very rich, and, as can be seen in figure 3, the vessels often show hypertrophy of the adventitial elements.

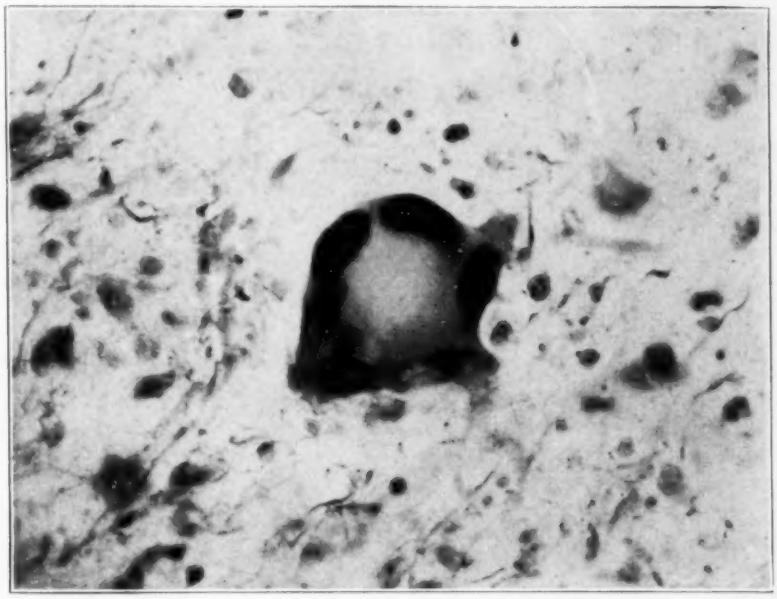

Fig. 4.—A multinucleated tumor cell with its processes showing the astrocyte-like form. Silver carbonate method of del Rio-Hortega.

Comment.—The tumor, then, consists of a diffusely infiltrating glioma involving the frontal lobe and the corpus callosum. The callosal portion consists largely of astroblastic and astrocytic elements. The cortical portion consists of embryonic spongioblasts and astroblasts, with a scattering of hypertrophic astrocytes, spread among which are large numbers of giant cells of astrocytic origin; nerve fibers are well preserved, neuroglia fibers are present, and vessels are abundant.

DEVELOPMENT OF GIANT CELLS

The large numbers of giant cells in the tumors studied offered an opportunity to study the various stages in the development and dis-

integration of these cells. This has been well done previously by Achucarro. By means of the silver-carbonate technic, it was possible to study carefully certain obscure factors in the genesis of these large cell elements.

Formation of astrocytic giant cells takes place by means of amitotic division of the nuclei, with or without an accompanying hypertrophy of the protoplasm. Sometimes there is a concomitant enlargement of the protoplasmic structure. Often the latter remains scanty.

Fig. 5.—A giant cell wrapped around a capillary vessel. Silver carbonate method of del Rio-Hortega.

The first visible evidence of division of the nuclei is seen in the lobulated stage. This may occur in simple fashion, with an indentation of the nucleus at one point, or it may be more complicated, with multiple indentations around the periphery of the nucleus. In figure 7 is seen a nucleus with beginning lobulation at *A* and completion of the division at *B*. In figure 8*A* is seen a nucleus with indentations in the periphery in a very early stage of lobulation. Figure 8*B* shows a further stage of the process, with the clumping of the chromatin preparatory to the splitting off of portions to form new nuclei. The process has

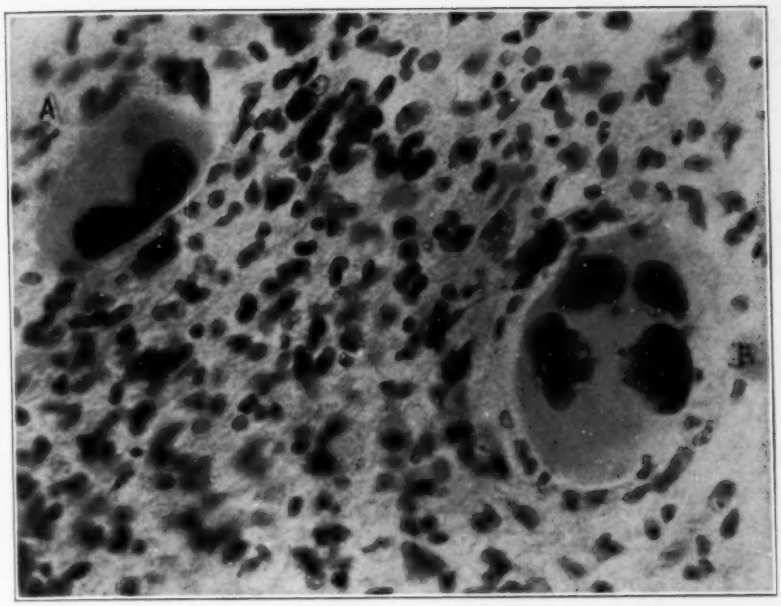

Fig. 6.—Two cells representing different stages in development of the giant cell. At *A* there is simple indentation of the nucleus. At *B* the process has progressed to the formation of four separate nuclear masses. Silver carbonate method of del Rio-Hortega.

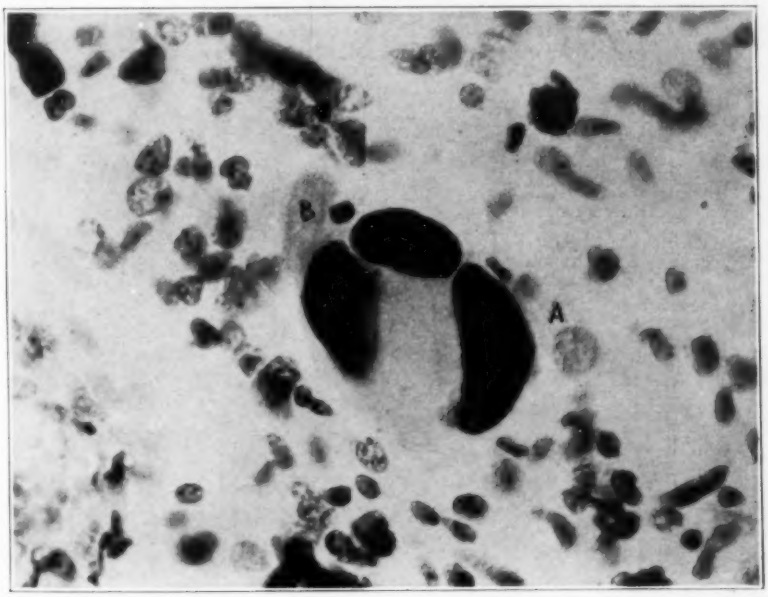

Fig. 7.—A tumor giant cell showing at *A* a whole nuclear mass; a further stage of the development of the mass is seen in the division into two nuclei (*B*). Silver carbonate method of del Rio-Hortega.

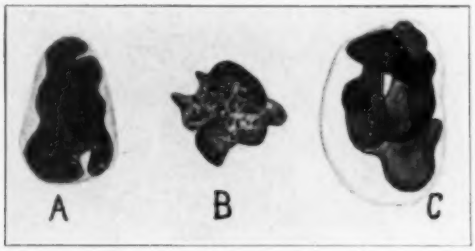

Fig. 8.—Nuclei undergoing amitotic division. In *A*, there is merely indentation of the nuclear surface. In *B*, lobulation is evident. In *C*, the separate nuclear masses are beginning to separate from the nucleus.

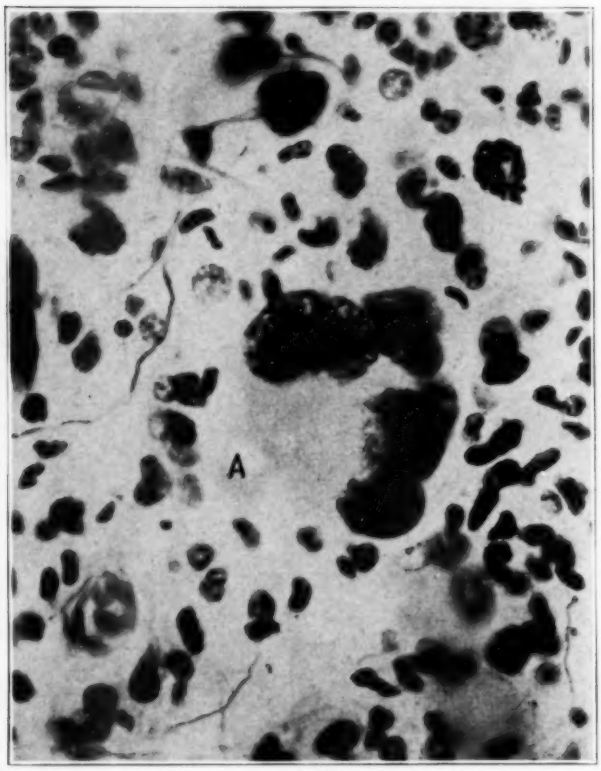

Fig. 9.—A tumor giant cell showing the amitotic division of the nucleus to form a multinucleated cell. Silver carbonate method of del Rio-Hortega.

developed a step further in figure 8*C*, which shows several portions of a single nucleus about to be set free as independent nuclear elements.

Following lobulation, the various elements separate from the single nucleus and become independent nuclei. The number of nuclear elements will depend on the amount of division that has taken place. In figure 6*B* there are only a few nuclei present after lobulation and division. Figure 10, however, shows a number of nuclei that practically fill the cell and surrounded it in its periphery. As the nuclei divide and fill the cell, they tend to form a crown or roset effect, as indicated in figures 10 and 11*D*. In the latter illustration, the various nuclear elements can be seen to radiate more or less toward a central structure.

As the nuclear elements divide and multiply, they can be seen to be connected by definite filaments. A group of cells with such filments is seen in figures 2*B*,

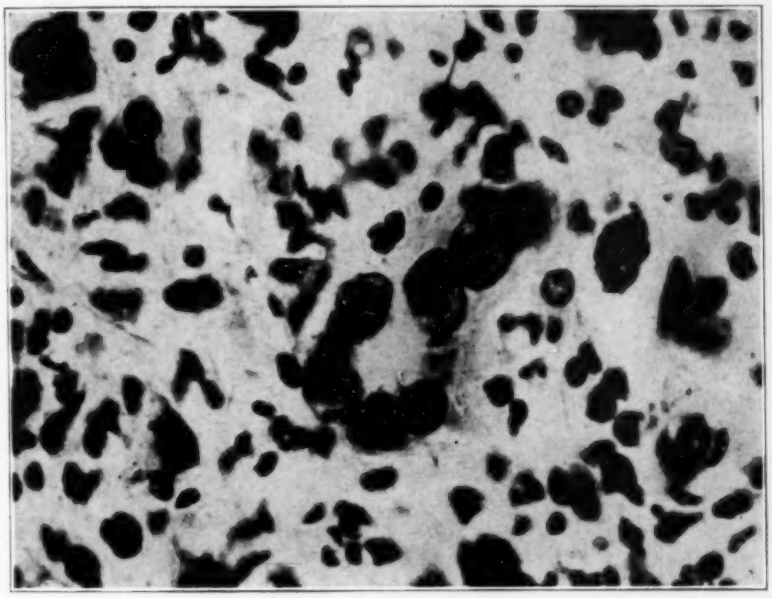

Fig. 10.—A further stage in the development of a multinucleated giant cell, showing more numerous nuclei. Silver carbonate method of del Rio-Hortega.

11, 12, 13 and 14. In figure 11*A* two filaments are seen formed, as it seems, by a sort of stretching out of the newly formed nuclei. Figure 11*B* shows two nuclei connected by a series of filaments leading to a poorly defined central structure which probably represents the remains of old chromatin material. More complicated filamentous arrangements are seen in figure 11*C* and *D*. The latter cell still retains its vascular foot, which is greatly hypertrophied. In figure 12*A* are seen a number of fine filaments leading out from nuclei arranged in a crown effect to a central connecting point. The same is true of figure 12*C*, while 12*B* shows nuclei connected one with another by means of filaments. In figures 13 and 14 are depicted complicated filamentous arrangements which are arranged in a circular effect. In both figures 13 and 14, the concentration of the filaments onto a central ill defined mass is very clear. In figures 2*A* and *B* are seen very good examples of the filamentous connections of these giant cell nuclei. In

figure 2*B* are at least twelve nuclear elements arranged coronally around a large cell, sending forth filaments to a central mass of granular material.

As can be seen, the filamentous arrangement of the nuclei varies from a relatively simple one, as in figures 8*A* and *B*, to very complicated arrangements,

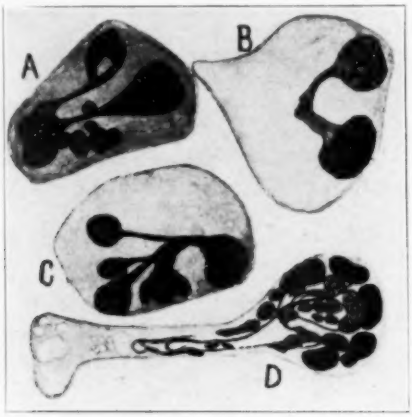

Fig. 11.—The method of division of the nuclei. At *A* the nuclear masses are connected by broad bands. At *B* they have a fibrillar structure. At *C* the division has gone on to a further stage, with the nuclei still connected by broad bands. *D* shows a still further stage, with the nuclei connected by fine filaments. The astrocytic shape of the cell is seen at *D*, with its swollen sucker process and foot

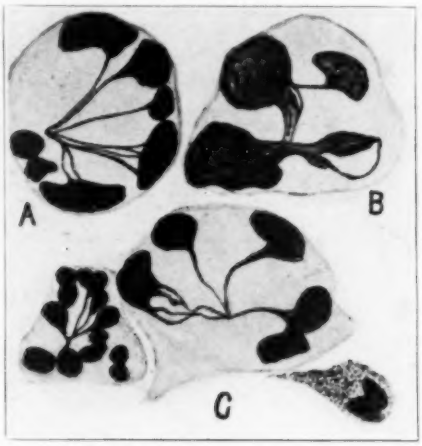

Fig. 12.—*A*, *B* and *C*, nuclei in the process of division, connected by the fine filaments leading down to a central point.

as in figures 2*B*, 11*D*, 12*A*, 13 and 14. The effect is of a number of nuclear elements connected by fine to coase filaments that converge on a central point, which in most cases is ill defined but which in some instances may be clear, as in figures 12*A* and *C*. The nature of these filamentous nuclei is more or less

puzzling. Achucarro believed that these are not multiple nuclei, but rather a single nucleus in the form of a roset, with peripheral buds which have acquired considerable importance but which are still dependent one on the other through a common center. The latter structure he looked on rather as the old nucleolus or centrioles of the original nucleus. That these various nuclear elements are more or less dependent one on the other is apparent when one views their rich filamentous connections. It is hard to believe, however, that they draw vital nourishment from a common center which morphologically appears far from vital. The filaments are probably formed by amitotic division, an early stage of which is

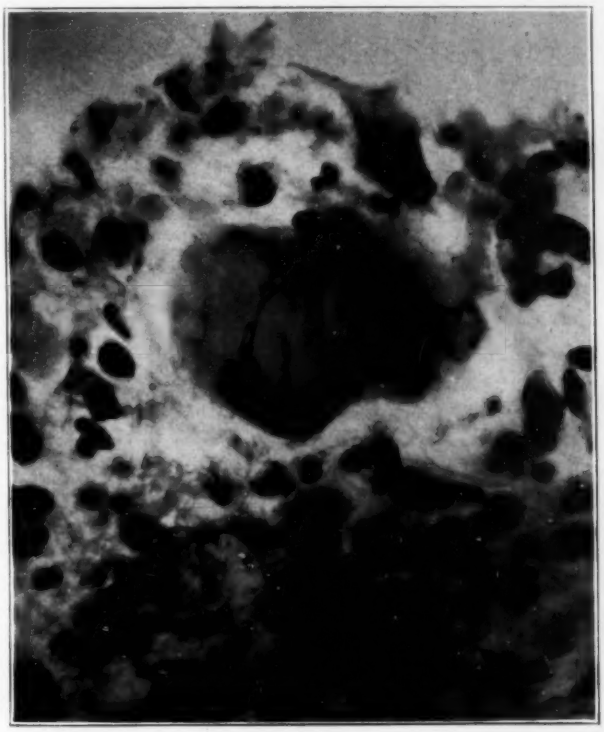

Fig. 13.—The nuclear masses of a tumor giant cell connected by fine filaments. Silver carbonate method of del Rio-Hortega.

seen in figure 11*A*, and later stages of which appear in figures 11*B* and *C* and 12*B*. In the early stages of this process there is possibly some vital relation between the new nuclei and the common center, but this relation is lost in the later stages. Following the filamentous connections of these nuclei, there comes a stage when the various nuclei are independent.

Degeneration of the giant cells occurs first with a fraying of the nuclei. Then follows a vacuolization of the nuclei, as depicted in figures 15*A* and *B*. In the frayed stage the nuclei are pyknotic and dark or more or less homogeneous, with irregular, frayed edges. When they have become vacuolated they contain numerous well defined vacuoles.

After vacuolization, degeneration takes place in earnest. The first stage in this process seems to be a reticulation of the nuclei which are pyknotic and structureless. In figure 15*C* the reticulation of the nucleus has just begun. It is more advanced in *D*, *E* and *F*, and in *G* is even more advanced. In *H* and *I* the process has gone on to fragmentation, which is the final stage of disintegration of the nuclei. This is shown in figure 16; *A*, *B* and *C* show beginning fragmentation of the nuclei, while at *D*, *E*, *F* and *G*, the fragmentation of the nuclei is almost complete.

COMMENT

Giant cells in gliomas are not confined to a single type of tumor. Their presence is frequent in tumors of embryonic structure, such as

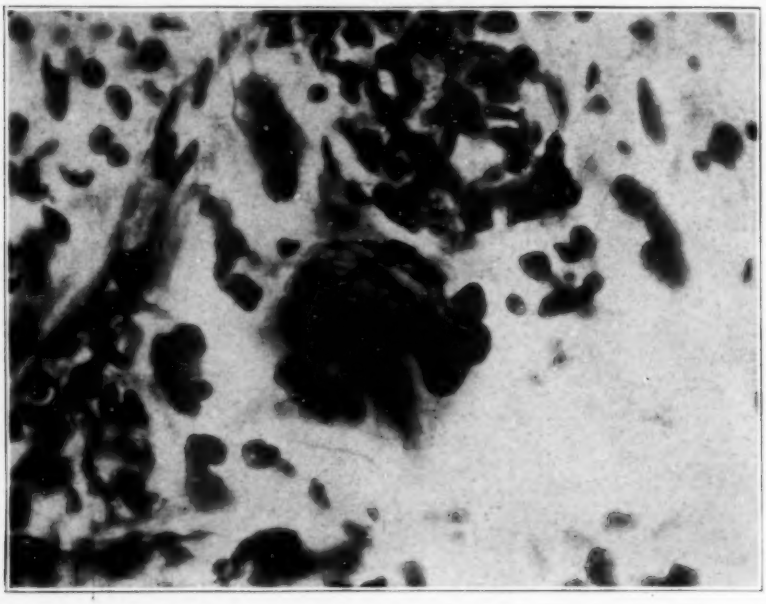

Fig. 14.—A similar cell with coarse and fine filaments. Silver carbonate method of del Rio-Hortega.

the spongioblastomas and astroblastomas, and also in some more differentiated tumors, as the astrocytomas. They are true astrocytic giant cells representing gliocytes, which by amitotic division of their nuclei, under the influence of the neoplastic growth, have failed to reach mature development. The frustration of the completion of normal division of gliocytes results in the formation of giant cells. Whereas in the normal gliocyte, cell division is complete after the partition of the nucleus and protoplasm into two portions, in the giant cell the nuclear division goes on to a more complicated division, frustrated, as it were, in its attempts to divide normally.

Fig. 15.—Giant cell nuclei undergoing degeneration, with vacuolation (*A* and *B*), reticular formation (*D*, *E*, *F* and *G*) and granulation (*I*).

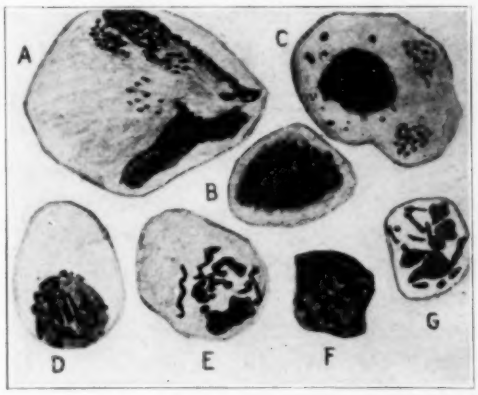

Fig. 16.—Giant cell nuclei (*A*, *B* and *C*) undergoing degeneration chiefly by granulation, and the breaking up of the nuclei into clumps of chromatin (*D*, *E*, *F* and *G*).

There seems to be a fairly clear analogy between the giant cells that are found in tumors of the brain and those present in gliosis, since in the latter process an overgrowth of glial tissue is often accompanied by the presence of giant cells. Rio-Hortega [9] has described the presence of monstrous gliocytes, with many nuclei and with numerous thick tuberous expansions, in the subependymal region in senility and arteriosclerotic dementia. The enormous neuroglia cells found in this location, exceeding in size the largest monster cells, at times have a body that fills the entire field of an oil immersion lens. The giant gliocytes in tumor of the brain and gliosis differ fundamentally, however, in that in

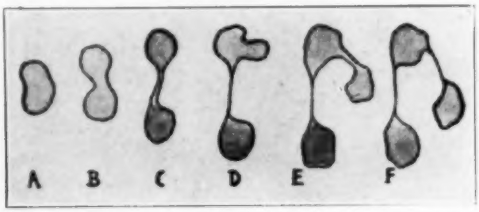

Fig. 17.—Simple method of amitosis of astroblastic nuclei to form tumor giant cells.

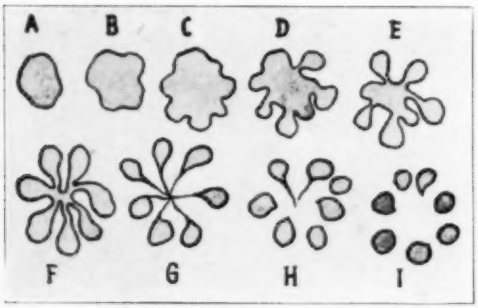

Fig. 18.—More complicated amitotic division.

the former process the giant cells represent not mature astrocytic elements, but immature gliocytes, frustrated in the act of proper division; whereas the giant cells in gliosis are always adult forms. There is the further difference that gliosis is accompanied by the overgrowth of many more neuroglia fibers than tumor. In Achucarro's case practically no neuroglia fibers were present. In the case that I have dealt with they were present in small numbers.

Certain observations suggest a trophic influence in the formation of giant gliocytes. In Rio-Hortega's case, giant cells were found to be

9. del Rio-Hortega, P.: Gliosis Subependimaria Megalocitica, Rev. de med. y cirug. **8**:85 (July) 1927.

largest just below the epidermis, a fact that suggested to him a trophic influence of cutaneous origin whereby the connective tissue formations of the skin in contact with isolated gliocytes excited the anomalous growth of the latter. A similar influence would seem to prevail in the present case, in which most of the giant gliocytes were arranged either in contact with the vessels or in their immediate vicinity. Most of these vessels exhibited marked adventitial proliferation and infiltration, so that the presence of giant cells may have been in response to connective tissue stimulation or to the same influence that was responsible for the adventitial hypertrophy and infiltration. On the other hand, the presence of the giant cells in considerable numbers in glial tumors of certain types suggests the possibility that in such tumors there may be some intrinsic stimulus peculiar to the tumor itself which excites the presence of giant gliocytes. The same may be true of the subependymal gliosis in senility and arteriosclerotic dementia as described by Hortega, in which there is no vascular proliferation and no direct contact with connective tissue.

Under the influence of a trophic stimulus, the nature of which is not entirely clear, gliocytes are stimulated to form giant cells. The first stage in this process consists of a lobulation of the nucleus, which may be a very simple or a relatively complicated process, as can be seen in figures 8*A* and *C*, 17*A* and 18*A*. Following the lobulated stage the cell contains multiple nuclei, the number of these depending on the amount of nuclear division that has taken place. This may vary for different cells, as may be seen in figures 17 and 18. In the former, the cell divison may terminate at *D* and result in relatively few nuclei, or it may go on to *F* and result in several nuclei. The number of nuclei will not be as great as in the division pictured in figure 18. There then ensues a stage in which the newly formed nuclei are spread in coronal or roset fashion in the protoplasm, with filaments connecting each nucleus (fig. 18*C*). Following this there is a further stage in which the nuclei are independent of one another (fig. 18*D*). Achucarro believed that the various nuclei in the filamentous stage were dependent on one another. Reference to figure 18 will reveal that this is hardly probable. The filaments, formed as it were by a stretching out of the original nucleus, are connected at a central point which represents the remains of the old nucleus, but which is without vital function. It can easily be seen that in the stages represented by figures 17*B* and *C* and figure 18*B*, the various portions of the nucleus are dependent on the original nucleus for life, but by the time the filamentous stage is reached this vital connection is past. Soon after this, the various nuclei assume an independent existence.

Following this are seen the giant cells that have been described with a frayed nucleus and giant gliocytes with vacuolated nuclei. The former

are pyknotic, with irregular, uneven borders that appear finely ragged. Both these ragged and vacuolated nuclei represent transition stages between the vital giant nuclei and the frankly regressive gliocytes. Regression has begun in them, but vital function still remains. The life of the giant gliocyte is terminated by frankly regressive stages beginning with a marked pyknosis which leaves the nucleus almost structureless. This is followed by reticulation of the nucleus and by fragmentation with the formation of pseudomitoses and total destruction of the nuclear structure.

CONCLUSIONS

The mechanism of the multiplication of multinucleated cells may be interpreted as follows: In the simplest case (figs. 17*A*, *B* and *C*) the gliocyte tends to divide amitotically, the nucleus acquiring a bilobar form, dividing into two portions without losing its union and with a connecting filament more or less persisting between the two nuclei. The process in this case consists of a simple frustrated amitosis, in that the nucleus does not divide completely, nor does the protoplasm take part in the division. In the most complicated case (fig. 18) the nucleus of the gliocyte acquires a dumb-bell shape, becomes multilobulated as in *A* (with regular or irregular lobulation), and acquires a roset form.

Each one of the lobules tends to separate from the center, becoming sessile and pyriform successively (*B*), in order finally to become isolated (fig. 18*D*) or to persist united to its homologs by more or less long filaments (fig. 18*C*). Between the two extreme types there exist all sorts of transitions. In summary, therefore, one may consider the formation of multiple nuclei as a phenomenon of amitosis, which is frequently frustrated before total separation of the nuclei and before division of the protoplasm takes place.

SUMMARY

1. Attention is called to the preponderance of giant cells in some types of glioma.

2. The presence of giant cells in others gliomas is discussed.

3. A spongioblastoma multiforme with numerous giant cells is described.

4. The origin and development of giant cells in gliomas is described in detail, based on a study of these cells in a spongioblastoma and in astroblastomas and astrocytomas.

SCHILDER'S ENCEPHALITIS PERIAXIALIS DIFFUSA

REPORT OF A CASE IN A CHILD AGED SIXTEEN AND ONE-HALF MONTHS *

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School of Medicine
BOSTON

This report is made to emphasize the care needed to separate cases of macrocephalus due to diffuse degeneration of the brain from those due to hydrocephalus or tumor, with which they might become confused.

REPORT OF CASE

History.—A white male child, born in Roxbury, Mass., was first seen in the outpatient department when 10 weeks of age. The complaints were: vomiting, constipation and failure to gain weight. There were a discharge from the nose, redness of the left ear drum and a slight rachitic rosary over the ribs. Nothing, however, was known of the birth history or early development. At 9 months, he was again brought to the outpatient department, when it was noted that the anterior fontanel was tense, and that there was a fine vertical nystagmus, a weak action of the left external rectus and a dull note on percussion of the head, which measured 17¼ inches (43.12 cm.). Since at birth the normal head measures 34 cm. (Holt) or 35 cm. (Sachs), and at 1 year, according to Holt, boys' heads measure 45.9 cm., the head of this child was not too large for the age at this time, though if general nutrition were poor it might have looked out of proportion to the body. (Dr. R. C. Eley, house officer at the time, confirmed this idea.)

On the next visit, a month later, the nystagmus was again noted, and the head measured 19¾ inches (48.375 cm.), an increase in size of 5.25 cm., which is distinctly pathologic, since a gain of more than 3.0 cm. per month is considered a danger signal; this was the greatest difference in enlargement noted in the history. Cod liver oil and sunlight were prescribed.

At 11 months, though the nystagmus was still present, it seemed as though there had been improvement (due to cod liver oil and sunlight?), for the child grasped at objects, an activity of the fourth month usually, and attempted to hold up his head, also an activity of the fourth month period. The head now measured 20 inches (50 cm.), the normal circumference of the head of a boy aged 4.

When the child was 1 year of age, vomiting was again a complaint, the anterior fontanel was tense, and there was a suggestion of a Kernig sign. The eyegrounds showed no evidences of pressure or degeneration, and the measurement of the head had subsided slightly to 19¾ inches (48.375 cm.). Two weeks later, the complaints were constipation, vomiting, pain and nystagmus, and the head again measured 20 inches (50 cm.).

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* Submitted for publication, July 25, 1930.

* From the Children's Hospital and Department of Pathology, Harvard University Medical School.

At 13 months, a lumbar puncture was done and showed a pressure of 350 mm. of water; the head now measured 20½ inches (51.25 cm.).

A 14 months, an examination of the fundi suggested optic atrophy, nystagmus was present, and the head measured 20½ inches (51.25 cm.), just as it had the previous month. In another six weeks, when the boy was 15½ months of age, roentgenograms were made of the head, and the report read "suggestive of hydrocephalus" (this was explained as meaning a separation of sutures); there was beginning optic atrophy and the head measured 20¼ inches (50.625 cm.), perhaps because a different examiner had measured it, perhaps because the measurement was taken during a moment of quiet.

The child was admitted to the hospital on Jan. 17, 1927, at 16 months of age; he could not sit up or even hold up the head, though children usually do the latter

Fig. 1.—Roentgenogram of child's head at 15½ months of age; the head measured 20¼ inches (50.625 cm.). The picture was taken and presented by Dr. Charles E. Vogt.

at 4 months of age. He appeared retarded mentally, and it was questionable whether he saw objects. He tried to talk. There was a convergent strabismus and the left optic disk could not be seen, though the right was sharply outlined. The Kernig sign was positive and the knee jerks were increased. The urine showed nothing of note; examination of the blood revealed: hemoglobin, 75 per cent; red blood cells, 6,140,000; white blood cells, 8,800, and a low percentage of polymorphonuclears (25 per cent). Lumbar puncture registered a slightly increased pressure; the fluid contained only 4 cells. A tuberculin test was negative. There was a daily mild rise in temperature, which increased to 106 F. just before death. No focus of infection was determined clinically.

Autopsy.—This was performed eight hours post mortem by Dr. M. J. Schlesinger, and showed bronchopneumonia and a brain that was large and soft

and weighed 1,890 Gm. after three days in formaldehyde. There was an excess of fluid in the subarachnoid space, yellow in color; the pia-arachnoid was glistening and opaque in places, but showed no sign of exudate. One hemisphere bulged more than the other. The brain was immersed in formadehylde in order to be cut at the next clinical conference, at which time, thirteen days later, preparations were made to catch the expected ventricular fluid when the brain was cut (on the death certificate hydrocephalus had been given as the cause of death). The brain was sectioned frontally and showed a firm cortex, but a pink, soft, retractile white matter "resembling mucoid degeneration" (S. B. W.). The tentative diagnosis of hydrocephalus could not be substantiated; there was no dilatation of the lateral

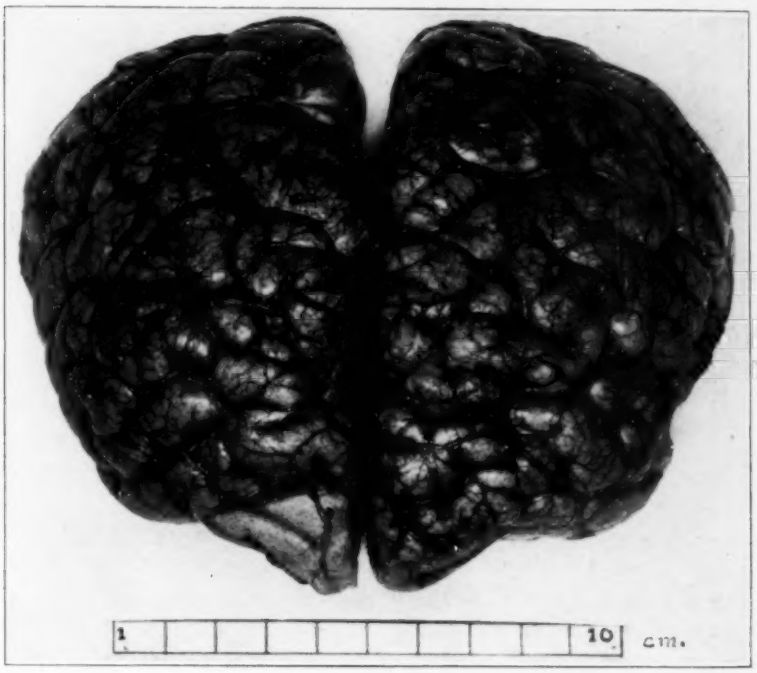

Fig. 2.—Brain tipped to show orbital portions of the frontal poles; it suggests pressure forward and downward.

ventricles, and the weight of the brain, 1,890 Gm., must have been due to the change in the white matter.

Drs. Wolbach and Schlesinger presented the brain to the Museum on April 18, 1927, and certain observations on the gross description of the brain were added.

The cerebellum weighed 150 Gm.; its greatest width was 10.8 cm., and it presented a rather pale surface. The vessels had a pressed-into-the-substance appearance, as is seen in any encephalitis. The pia-arachnoid was practically invisible and the whole cerebellum, though in formaldehyde for almost three months, seemed soft to the touch. The internal surface, on slicing, showed the whole white matter to have a pinkish cast, and the dentate nuclei were not visible. In a slightly uneven section, owing to the lack of firmness of the cerebellum, the right hemisphere

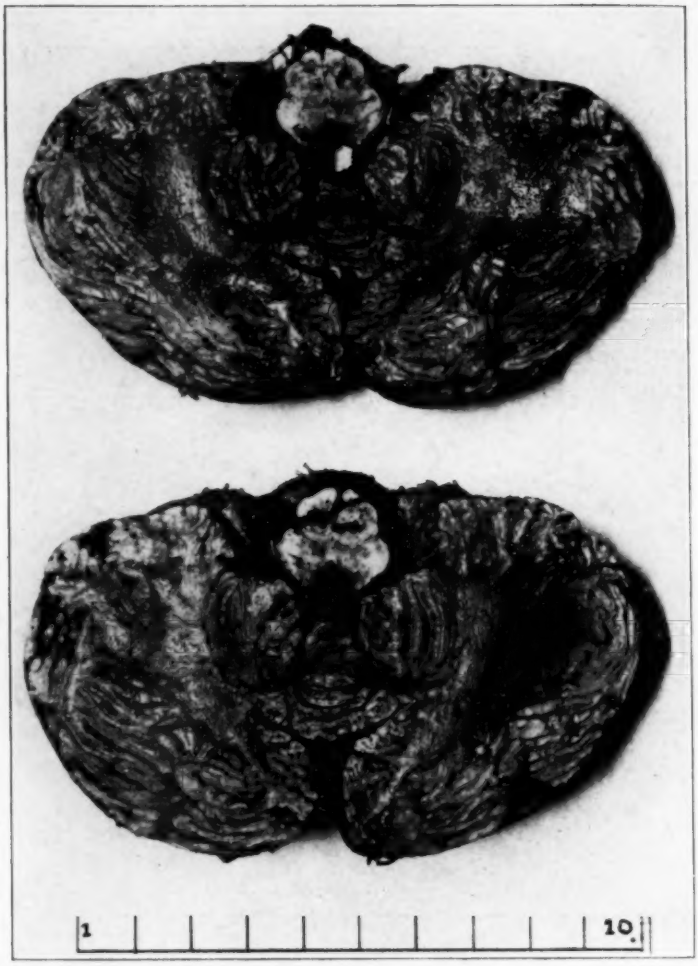

Fig. 3.—The cerebellum; note the softened retractile appearance of the white matter; compare with the drawing. Dentate nuclei are obscured.

Fig. 4.—Horizontal sections of the occipital lobes. Note the complete softening of the white matter as evidenced by its retraction from the cortex.

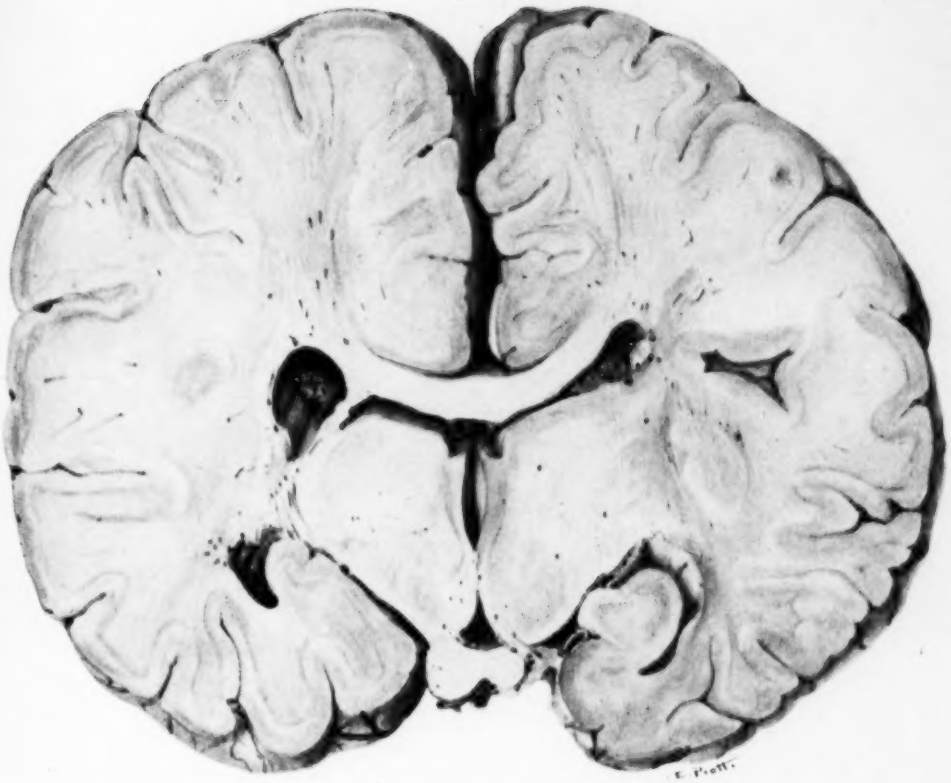

Fig. 5.—Drawing at the level of the third ventricle of the cerebrum. Note that the corpus callosum is not involved in the change indicated near the periphery.

Fig. 6.—Drawing of the cerebellum made after three months in formaldehyde. Note the pink cast of the white matter.

Fig. 7.—Section near the occipital tips. Note that the process is more marked above the ventricles.

Fig. 8.—Weigert section showing loss of myelin sheaths at the periphery of the white matter and preservation within.

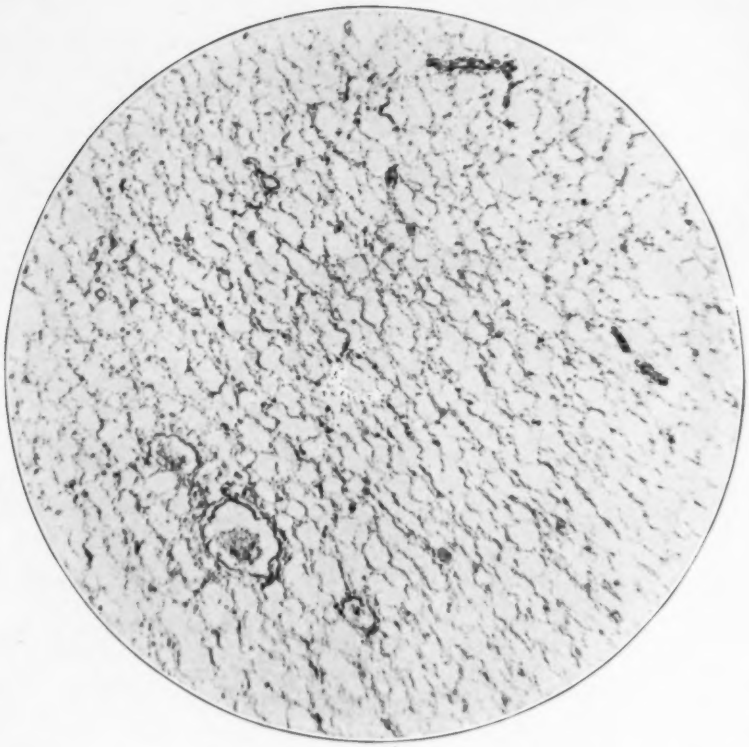

Fig. 9.—Section of the white matter of the cerebrum, showing extreme edema and no reaction about the blood vessels. Cresyl violet stain; × 95.

Fig. 10.—Section of the cerebellum, showing edema of the granule layer and preservation of the cortex. C. V. stain; × 23.

was 0.6 cm. less in diameter than the left, and the edges of the folia seemed less well preserved than on the left. The consistency of the white matter was velvety and springy.

All of the gross sections through the brain were the same: the gray matter apparently was intact, with pink retractile white matter; this appearance was more marked in the posterior portion of the brain and above and lateral to the ventricles, which were either normal in size or somewhat reduced.

Microscopic Examination.—With the simpler stains (cresyl violet, hematoxylin and eosin, and Weigert) the white matter near the cortex showed as a mass of

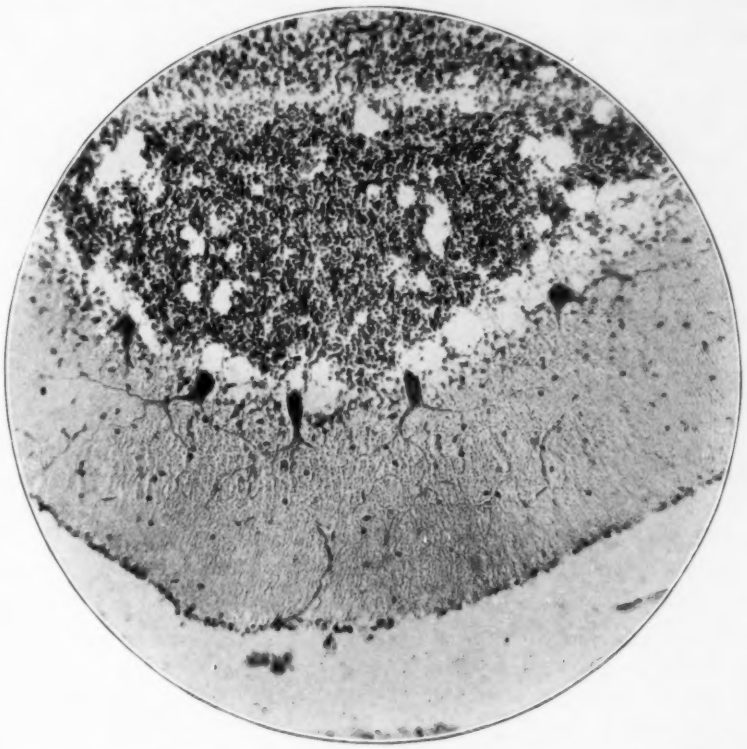

Fig. 11.—Section of the cerebellum, showing the preservation of Purkinje cells, usually very sensitive to infections and toxins. C. V. stain; × 122.

lacy edema with glia cells fairly well preserved, but not in excess. There were no perivascular changes and no evidence of any cellular reaction to the process in the subcortical regions. Frozen sections stained with scharlach R showed no fat, except an occasional trace in the vessel walls. At a point where the white matter was preserved, bordering on the active pathologic process, there were smaller lacunae of edema, but otherwise no changes. In the cerebellum the process was marked, involving the granular layer, but strangely (considering their supposed sensitivity to toxins) the Purkinje cells were well preserved. A section through the medulla showed a moderate edema of the white matter.

COMMENT

To July 1, 1929, there appeared in accessible printed form reports of twenty-eight cases of encephalitis periaxialis diffusa, first named and described by Schilder of Vienna, in 1912. Symonds [1] reviewed the disease in the order of the known cases, and pointed out that in 1902 Collier and Greenfield had observed a case post mortem in which diffuse degeneration of the white matter in the brain was present, but had not published the observation. Haberfeld and Spieler observed such a case in 1910, and pointed out the familial incidence, but it was Schilder, in 1912, who named the disease in the stage when the medullary sheaths were attacked, leaving the axon intact, "periaxialis diffusa." In 1914, Marie and Foix studied another such case (the first patient to recover from this disease; he died ten years later of tuberculosis). Krabbe, in 1916, described such a condition under another name. In 1924, Bauman, Collier, Greenfield and others wrote of it. It is stated that it may be familial, may commence at any age, may rapidly or slowly progress or may become arrested.

Schaltenbrand,[2] in a digest of the cases published, summed up the clinical reports as showing that the disease occurs in patients of any age but particularly in those under 20, beginning with apathy and blindness, and followed by symptoms that point to focal disease in the hemispheres. Symptoms of brain tumor, optic neuritis, vomiting and headaches arise. There may be epileptic convulsions. Before death, spastic paralysis of the extremities, blindness and loss of speech complete the picture. The duration is given as from a few days to several years. Only one recovery, and that with mental defect, has been noted. Rarely has the diagnosis been made before death. Pathologically, the white matter is degenerated (more than described by Schilder), and there may be evidences of scavenger cells and increase of glia. There is no known cause or treatment.

From a review of the published cases, the usual chronological sequence of reactions to the description of an entity noted was: surprise, consideration, refutation, imitation, renaming, subdivision and finally acceptance, with reservations and exceptions.

The history in my case shows that at 10 weeks the child had a red ear drum and nasal discharge, the only signs of an infection until the last two weeks of life, when the temperature rose to 106 F. before death. One may suppose that the general nutrition was not good, since at 10 weeks a slight rosary was found, and the mother complained

1. Symonds, C. P.: Encephalitis Periaxialis Diffusa: Schilder's Encephalitis, a Critical Review, Brit. J. Child. Dis. **25**:83 (April-June) 1928.

2. Schaltenbrand, G.: Schilder's Encephalitis Periaxialis Diffusa: A Case Report with Anatomic Studies, Arch. Neurol. & Psychiat. **18**:944 (Dec.) 1927.

that the baby did not gain. At 9 months, a slight increase in the size of the head for the age was observed in an examination made in the outpatient department. From then on, an increase in size of the head was continually observed, and this naturally led to the mistaken diagnosis of hyrocephalus, the roentgenographic report concurring in this because of separation of the sutures. It would be well to remember that there are persons with congenital macrocephalia as well as those with congenital microcephalia, and that a head can grow because of massive enlargement of the brain without pathologic collections of fluid.

If this brain became edematous because of the possible infection at 10 weeks, there were no vascular residuals to suggest it.

Collier's [3] clinical dicta are frequently quoted in reference to the short onset of the disease, the progressive course, the possible remissions, the duration from a few months to three years, the cerebral blindness, mental reduction, spastic paralysis and deafness, but, as Bauman [4] pointed out, no widespread disease of the nervous system can have a predictable clinical picture, since no two cases are alike in extent of nerve tissue involved, or in the rapidity with which the lesion spreads.

Clinicians would do well to bear in mind this disease as a possibility, even if remote, when a patient (most frequently a child) is seen with signs of cerebral pressure with or without an enlarging head. Since the meninges are seldom involved and the lesion, whether degenerative or inflammatory, is found chiefly in the white matter, no increase of cells in the cerebrospinal fluid would be seen, and no stress has been laid on spinal fluid cell counts in the reported cases. The pressure of the spinal fluid may be of some value, being theoretically high, in differentiating the condition from hydrocephalus. The ventriculograms may be of value in showing the small size of the lateral ventricles. Even with separation of the sutures, macrocephalia must not be confused with hydrocephalus.

The prognosis seems to be bad; no clinical cases have been reported as encephalitis periaxialis diffusa—except one by Foix—death and autopsy being often the deciding factors in the diagnosis. This has been true previously in other obscure lesions of the brain, now happily less obscure. Therapy has as yet no real value, no means of restoring the dying nerve sheaths having been advocated, but once the etiology is clear, the therapy will improve.

SUMMARY

1. A male child, seen repeatedly from the age of 10 weeks to 16 months, died at 16½ months of age. Only at 10 weeks and during

3. Collier, J., and Greenfield, J. G.: The Encephalitis Periaxialis Diffusa of Schilder: A Clinical and Pathological Study, Brain **47**:489, 1924.

4. Bauman, L.: Encephalitis Periaxialis Diffusa, Brain **47**:453, 1924.

the last two weeks of life when in the hospital did he present evidences of infection.

2. During the last seven months of life he was known to have an enlarging head and signs of increased intracranial pressure.

3. The brain was soft and weighed 1,890 Gm. after three days in formaldehyde. There was a subcortical loss of myelin and a diffuse and marked edema of the white matter, with no vascular inflammatory reaction. The Purkinje cells, as well as cells in the cerebral cortex, were preserved.

4. As in other reported cases, no hint of the etiology can be given, except that in general one expects edema to be due to toxic action.

GANGLIOGLIOMAS

A FURTHER REPORT WITH SPECIAL REFERENCE TO THOSE OCCURRING IN THE TEMPORAL LOBE *

CYRIL B. COURVILLE, M.D.
LOS ANGELES

In a previous communication,[1] two cases of this supposedly rare tumor were described, and a résumé of the available reported cases was made. Particular attention was paid to the group of gangliogliomas [2] that have their origin in the floor of the third ventricle (tuber cinereum). Since the first report was submitted, another glioma of this type, occurring in the right temporal lobe, has been studied. In addition, further investigations have brought to light other reported cases of evidently typical gangliogliomas. In order to make the review of the literature more complete, as well as to describe this new case, this further contribution was undertaken.

Among tumors of the glioma group, gangliogliomas are almost certainly not as uncommon as reports in the literature would suggest. In a personally studied series of seventy gliomas, three such tumors have been found, as well as one or two others which seem to be transitional types closely allied to it. Furthermore, it is likely that many reported cases have been misinterpreted because careful histologic studies were not made. Tumors of the floor of the third ventricle, as described grossly

* Submitted for publication, June 27, 1930.

* From the Neurosurgical Service of Dr. Carl W. Rand, Los Angeles County General Hospital.

1. Courville, Cyril B.: Ganglioglioma, Tumor of the Central Nervous System: Review of the Literature and Report of Two Cases, Arch. Neurol. & Psychiat. **24**:439 (Sept.) 1930.

2. Many names have been given to this tumor in the past, but those of more recent favor are ganglioneuroma or ganglioglioneuroma. The nerve fibers in the tumor are now considered to be the product of the neoplastic ganglionic elements and an integral part of them, and it therefore seems that the use of the additional term neuroma is redundant. I have used the term ganglioglioma because it indicates the two essential elements found in the tumor. The name was first used by Ewing in designating the case of Perkins (Perkins, O. C.: Ganglioglioma, Arch. Path. **2**:11 [July] 1926), but he now seems to prefer the term ganglionic glioma (Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 440).

by Ley [3] and by Wakeley and Allen,[4] or as incompletely studied histologically in the case of Schnyder,[5] would possibly fall in this group. Another source of confusion has been the introduction of the term "neuroglioma gangliocellulare" in describing the lesions of tuberous sclerosis as reported by Baumann, Hartwegen, Ziegler, Findlay and others. Instead of designating a glioma the tissues of which contain neoplastic ganglion cells, the term refers to what are evidently congenital heterotopias.

From a critical study of certain cases appearing under suggestive titles or buried in articles on gliomas in general it seems evident that the cases of McKennan and Proescher,[6] Katzenstein,[7] Josephy [8] and

3. Ley, Rodolphe: Tumeur de l'infundibulum (tuber cinereum), intégreté de l'hypophyse, syndrome adipeux, Rev. neurol. **38**:377 (April 22) 1922.

4. Wakeley, C. P. G., and Allen, I. M.: Secondary Hydrocephalus as a Factor in the Diagnosis and Localization of Intracranial Tumours, with its Investigation and Treatment, Brit. J. Surg. **17**:278, 1929. In 1885, Hale White reported a case under the title of "A Myo-Neuroma of the Pituitary Body" (Tr. Path. Soc. London **36**:37, 1885); this tumor has been considered as a ganglioneuroma by Hosoi (Hosoi, K.: Teratoma and Teratoid Tumors of the Brain, Arch. Path. **9**:1217 [June] 1930). While the histologic description of the tumor was too brief for one to draw positive conclusions, the presence of striated muscle, myelinated nerve fibers and a small circumscribed group of ganglion cells, the absence of all microscopic evidence of neoplastic growth and the position of the tumor anterior to the hypophysis and about the chiasm seem to point to its teratoid character. Its presence may be accounted for by an abnormal development of the chiasmal region and the craniopharyngeal canal. It cannot be included with the typical gangliogliomas having their origin in the tuber cinereum in any case and is probably not a glioma of this variety.

5. Schnyder, P.: Ueber Gliom, Gliose und Gliomatose und ihre Beziehungen zur Neurinomatosis, Schweiz. Arch. f. Neurol. u. Psychiat. **23**:116, 1928. In this case a small tumor, 6 mm. in diameter, was found in the floor of the third ventricle, in which glia cells and fibers, unmyelinated nerve fibers and groups of "epithelial cells" were demonstrated histologically. In the short description of the microscopic appearance of the tissue, no mention is made of ganglion cells. Mutliple tumors of the nerve roots of the spinal cord were also found.

6. McKennan, T. M. T., and Proescher, F. R.: A Case of Neuroglioma Gangliocellulare of the Brain: Operation: Recovery, New York M. J. **88**:115 (July 18) 1908. While these authors believed this tumor to be identical with those appearing in the literature under this title (cases of tuberose sclerosis), the clinical history is that of a true new growth. A small, sharply demarcated, subcortical tumor was removed surgically from the right frontal lobe of a man, 39 years of age. Ganglion cells and glial cells of both embryonic and adult types as well as unmyelinated nerve fibers were found in histologic sections. The presence of mitotic figures in the cells indicated the neoplastic character of the tumor mass.

7. Katzenstein, Julius: Zur Frage der Ganglioneurome im Anschluss an einen Fall von Ganglio-Glioneurom des Grosshirns, Inaug. Diss., Wurzburg, 1910. A small tumor about the size of a walnut was found in the right temporal lobe

MacPherson [9] should be included in the list of accepted cases. While some of these tumors were not studied as exhaustively from a histologic standpoint as they might have been, the presence of immature as well as mature ganglion cells and glia cells embedded in a tumor stroma composed to a greater or less extent of nerve fibers seems to warrant their inclusion in the group. Furthermore, most of them fulfil many of the gross characteristics of the undoubted cases. Since my first contribution was submitted, Schmincke [10] and Bielschowsky and Simon [11]

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of an adolescent boy, who died after an illness of ten years, characterized by epileptiform seizures and abnormal mental and sexual development. Both immature and mature glia and ganglion cells were found embedded in a tumor stroma composed of glia fibrillae and unmyelinated nerve fibers. No mitotic figures were observed but amitosis was evident from the constriction and indentation forms and from the multinucleated cells.

8. Josephy, H.: Ein Fall von Parobulbie und solitärem zentralem Neurinom, Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:62, 1924. Although the author was more concerned with identifying the growth with peripheral neurinomas than of studying carefully the structure of the individual cells, it is likely that the tumor was a true ganglioglioma. This is suggested by the location and small size of the tumor, its association with cystic cavities, the presence of large nuclear forms containing round or oval nucleoli and the occurrence of unmyelinated nerve fibers. The patient was a woman, aged 22.

9. MacPherson, Donald J.: Studien über den Bau und die Lokalisation der Gliom, mit besonder Berücksichtigung ihres Missbildungscharakters, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **27**:123, 1925. This author describes a case in which a calcareous nodular tumor was found arising from the floor of the third ventricle and extending into the thalamus. Three types of cells were described: (1) sheath, (2) ganglion and (3) glia cells. While it had the appearance of a peripheral neurinoma, the occurrence of ganglion cells and glia cells marked the growth definitely as a ganglioglioma. The sheath cells were probably bipolar and unipolar glioblasts and neuroblasts which form the fibrous portions of these tumors. No clinical history of the case was given.

10. Schmincke, A.: Zur Kenntnis der Zirbelgeschwülste: Ein Ganglioglioneurom der Zirbel, Beitr. z. path. Anat. **83**:279, 1930. The author describes a tumor the size of a hazelnut arising from the pineal body in a man, aged 50. Ganglion cells, unmyelinated nerve fibers and glia cells and fibers were demonstrated histologically. Several other cases were cited from the literature in which elements resembling ganglion cells were found in pineal tumors, but they were evidently a casual and not a prominent observation.

11. In a personal communication from Professor Bielschowsky regarding one of his previous cases, he mentioned the reporting of a diffuse ganglioglioneuroma of the cerebellum before the Berlin Society for Psychiatry and Neurology. A description of the case, reported with Dr. Simon, has just made its appearance (Bielschowsky, M., and Simon, A.: Ueber diffuse Hamartome [Ganglioneurome] des Kleinhirns und ihre Genese, J. f. Psychol. u. Neurol. **41**:50, 1930). These authors referred to another case of this type reported by M. B. Schmidt (Ueber halbseitigen Riesenwuchs des Schädels und seine Beziehung zur Leontiasis und Ostitis fibrosa, Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres **23**:594, 1926): A man, aged 45, with marked proliferation of the bones of the left side of the

have reported other typical cases. In Schmincke's case a ganglioglioma was found arising from the pineal body, resembling in this respect the unusual tumor described by Horrax and Bailey. That of Bielschowsky and Simon proved to be a diffuse tumor of the cerebellum. In table 1 all of the reported cases that I have been able to find which seem to be gliomas of this type have been tabulated.[12]

This glioma may be considered as having its cellular origin in a primary indifferent element, from which stages up to the adult forms of neuroglia and atypical ganglion cells are differentiated. Its stroma is

TABLE 1.—*Gangliogliomas of the Central Nervous System*

No.	Author	Year	Age	Sex	Location of Tumor	Duration of Symptoms
1	Worcester	1901	42	M	Left parietal lobe	3 years
2	Dumas	1904	29	F	Right cerebral hemisphere	About 1 year
3	McKennan and Proescher	1908	39	M	Right frontal lobe	3 months
4	Schmincke	1910	17	M	Right temporal lobe	9 years
5	Katzenstein	1910	16(?)	M	Right temporal lobe	About 10 years
6	Pick and Bielschowsky	1911	24	F	Cervical cord and medulla	?
7	Achucarro	1913	20	M	Cerebellum	2 years
8	Schmincke	1914	17	M	Right temporal lobe	?
9	Robertson	1915	16	F	Tuber cinereum	About 1 year
10	Berblinger	1917	17	F	Septum pellucidum	?
11	Greenfield	1918	26	F	Tuber cinereum	About 3 years
12	Olivecrona: Case 1	1919	39	M	Right parietal lobe	8 days
13	Case 2	1919	?	F	Right frontal lobe	?
14	Lhermitte and Duclos	1920	36	M	Left cerebellar hemisphere	1 year
15	Josephy	1924	22	F	Tuber cinereum	5 years
16	MacPherson	1925	?	?	Tuber cinereum	?
17	Bielschowsky	1925	26	M	Multiple tumors	15 weeks
18	Perkins	1926	16	M	Tuber cinereum	3 weeks
19	Marinesco	1926	40	F	Tuber cinereum	?
20	Schmidt	1926	45	M	Left cerebellar hemisphere	10 years
21	Horrax and Bailey	1928	40	M	Pineal body	15 months
22	Bielschowsky and Henneberg: Case 1	1928	16	F	Left temporal lobe	11 years
23	Case 2	1928	11	F	Right temporal lobe	7 years
24	Courville: Case 1	1929	15	F	Tuber cinereum	Life (?)
25	Case 2	1929	Adult	?	Tuber cinereum	?
26	Schmincke	1930	50	M	Pineal body	6 months
27	Bielschowsky and Simon	1930	20	F	Right cerebellar hemisphere	2 years
28	Courville: Case 3	1930	35	F	Right temporal lobe	9 months

composed to a greater or less extent of unmyelinated nerve fibers. The presence of adult cell forms, in the light of present conceptions, indicates a more complete degree of differentiation and suggests the relative benignity of the tumor.

Grossly, the growth is usually small, and, while not sharply outlined in the sense of being encapsulated, it is fairly well delimited from

skull, died after an illness of ten years' duration with symptoms indicating increased intracranial pressure. At necropsy, a diffuse tumor of the left cerebellar hemisphere was found in which embryonic and adult nerve cells and nerve fibers were conspicuous. The tumor was designated as a hamartoma.

12. References to the cases in this table which do not accompany this article may be found in my previous communication (footnote 1) in which a brief résumé of the clinical record of each is given.

the surrounding brain. A further suggestion of its slow growth is indicated by the almost complete absence of distortion of surrounding structures unless the tumor is so situated as to cause obstructive hydrocephalus or is associated with a large cyst. Hemorrhages within the tumor may give it a mottled appearance which is further accentuated by areas of degeneration and small cysts. They have been found in almost every part of the brain but, judging from the reported cases, they are most commonly located in the floor of the third ventricle and in the temporal and parietal lobes.

REPORT OF CASE

Rapidly progressive course of intracranial pressure syndrome in a woman. Death nine months after onset. Small circumscribed glioma in right temporal lobe.

History.—A nurse, aged 35, was admitted to the neurosurgical service of the Los Angeles County General Hospital on Aug. 25, 1927, having been referred by Dr. Carl W. Rand, chief of the service. She complained of headaches in the right occipital region associated with nausea and vomiting of nine months' duration. A month prior to her admittance to the hospital she had noticed double vision and blurring of vision, particularly of the left visual fields. She proved to be extremely irritable and temperamental and refused to cooperate in the treatment. She insisted on leaving the hospital, and was discharged on August 28. She was readmitted to the psychopathic ward of the hospital on September 7, in a semicomatose condition.

Neurologic Examination.—At the time of her second admittance, examination revealed a bilateral choked disk, right exophthalmos, right internal strabismus, spasticity and marked tremor of the left arm with bilateral Babinski, Gordon and Oppenheim signs, all more marked on the left side. Percussion of the cranium gave a high pitched note suggestive of hydrocephalus. Permission for operative procedures of any sort was refused by the relatives, and, sinking into deep coma, the patient died on September 17.

Gross Pathology.—A necropsy was performed six hours after death by Dr. Lawrence Parsons who preserved the specimen for later study. On removing the calvarium, the cerebral convolutions were found to be considerably flattened and the sulcar markings partially obliterated. On removal of the brain, the right temporal lobe bulged out and was softer than the left. On coronal section, a reddish-gray, well circumscribed and apparently well delineated tumor mass was found in the right temporal lobe (fig. 1). The tumor apparently had its origin just ventrolateral to the hippocampus and had almost completely obliterated the inferior horn of the lateral ventricle. The tumor mass measured 2.8 by 2.6 cm. in cross-sectional diameters. The central portion of the tumor was largely degenerated and cystic and had a translucent appearance. The preserved marginal zone appeared rather mottled, evidently owing to small hemorrhagic extravasations. After fixation in a diluted solution of formaldehyde, the preserved areas had a grayish-yellow, brown or bluish color, depending on the situation.

The brain tissue surrounding the tumor was softer than normal and, on close inspection, was marked by curved fine striations parallel to the margin of the tumor. These striations were apparently caused by the compression of the softened adjacent brain tissue by the expanding tumor.

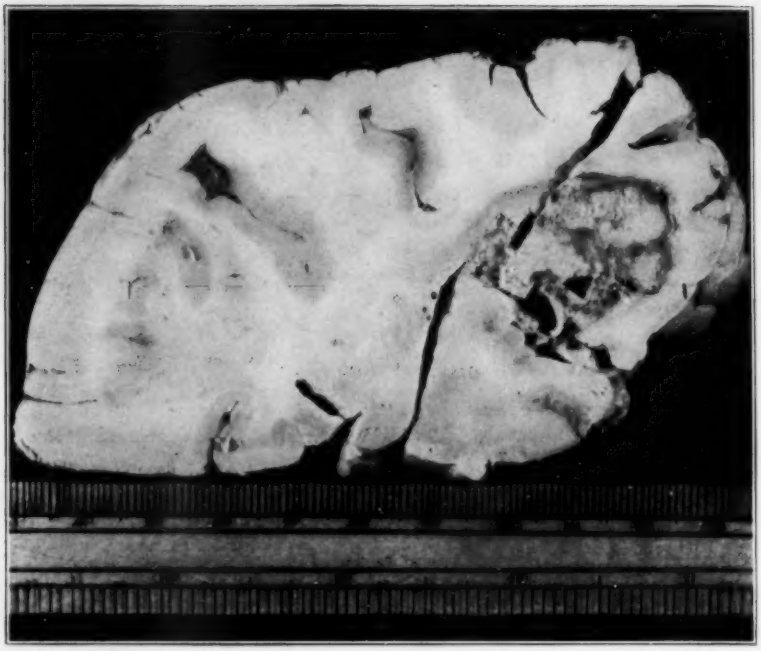

Fig. 1.—Ganglioglioma of the right temporal lobe.

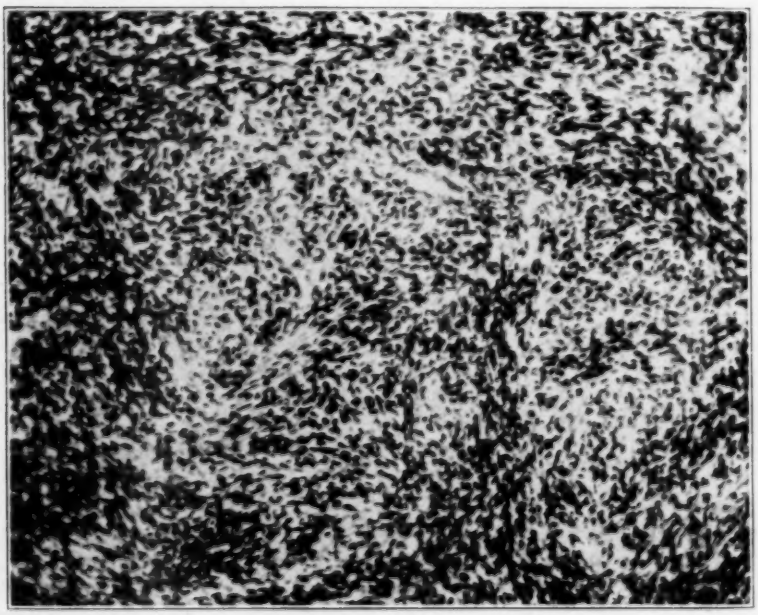

Fig. 2.—Neurinomatous structure of the tumor. Cajal's reduced silver method; × 95. In the very cellular areas only a few nerve fibers are found.

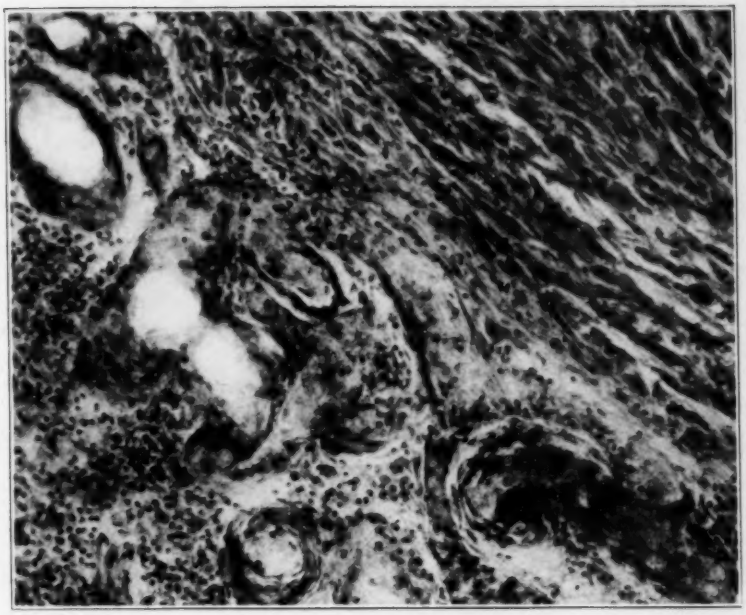

Fig. 3.—Sharply delineated margin of the tumor, large blood vessels and small round cell infiltration are shown. Hematoxylin and eosin stain; × 200. The fibrous character of the tumor is also shown.

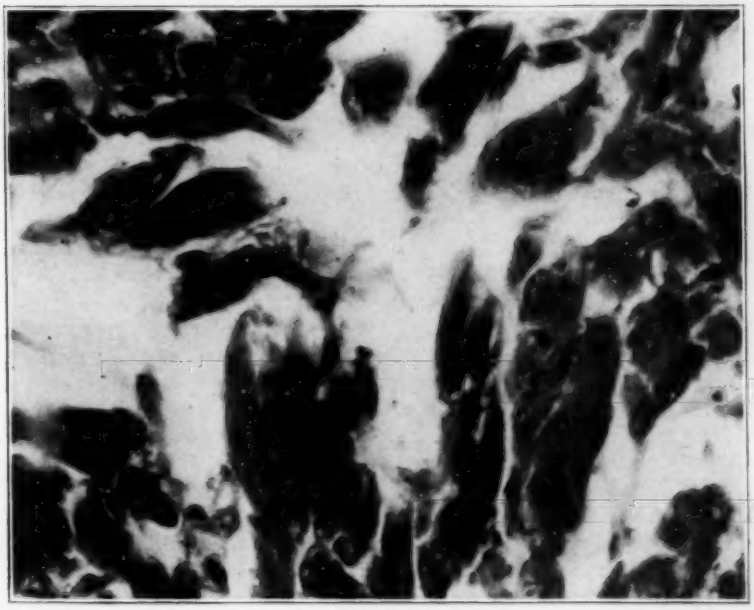

Fig. 4.—Marked variation in the size and shape of the cells is shown. Mallory's aniline blue stain; × 800.

Histopathology.—Blocks of tissue were taken from the tumor which had been fixed in a diluted solution of formaldehyde or subsequently in Zenker's fluid and stained or impregnated by the following methods: hematoxylin and eosin, phosphotungstic acid-hematoxylin, scharlach R and nile blue-sulphate for fat, van Gieson's, Mallory's aniline blue and Perdrau's methods for connective tissue, modified Wright's method for myelinated nerve fibers, Cajal's reduced silver method for unmyelinated nerve fibers and neuroblasts, Bielschowsky's method for neurofibrillae, Bielschowsky-Plein's stain for tigroid substance, Cajal's gold sublimate and Hortega's silver carbonate methods for glia, and Penfield's combined method for microglia and oligodendroglia.

Tissue Architecture and Cellular Morphology.—The tumor tissue proved to have no characteristic architecture and on the whole appeared to have a rather

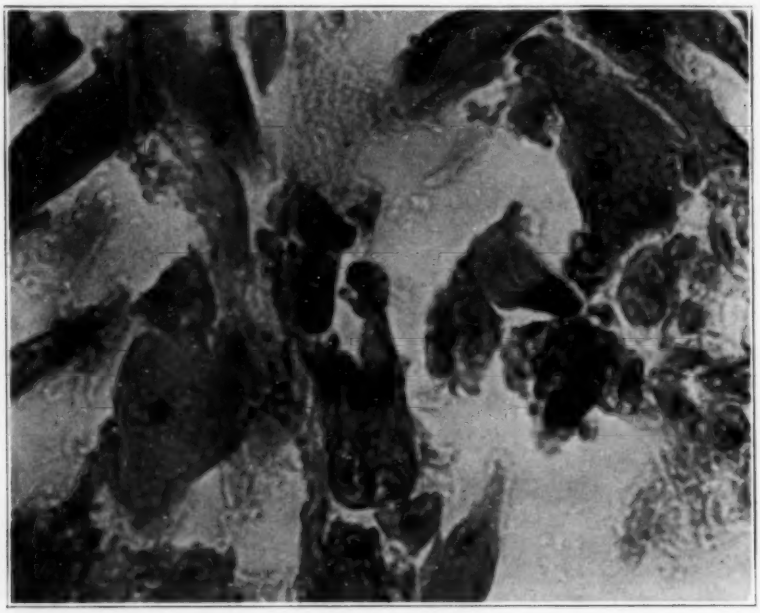

Fig. 5.—Vesicular nuclei containing nucleoli. Mallory's phosphotungstic acid-hematoxylin stain; × 1320.

fibrous structure. Irregular masses of cellular elements were isolated by transversely placed strands of fibers resembling at first sight the peripheral neurinomas (fig. 2). The tumor, while not definitely encapsulated, was fairly sharply outlined from the surrounding brain tissue, which was undergoing softening. Along its margin numerous large blood vessels were found (fig. 3).

From the standpoint of morphology, the cellular elements varied greatly in size and shape. From small, round forms, the cytoplasm of which was confined to a ring about the nucleus, up to large, multipolar and multinucleated giant forms could be found in a circumscribed field (fig. 4). Medium-sized cells were unipolar or bipolar, the processes extending for a variable distance in the section. The cytoplasm of the cells was, for the most part, finely granular, and evidences of hyaline and hydropic degeneration were not uncommon.

The nuclei likewise presented considerable variation in their size, shape and amount and arrangement of contained chromatin. In the smaller cells the nuclei were usually round or oval and had a well defined nuclear membrane and the chromatin was more or less evenly distributed throughout. In the larger forms, the nuclei were increased in size and had a thinner wall and the chromatin was usually condensed into a round, deeply staining nucleolus (fig. 5). Morphologically, these were characteristic of the nuclei of ganglion cells. Typical mitotic figures were frequently observed.

Of special interest in this connection was the occurrence of peculiar forms resulting from atypical or abortive attempts at cell division. Constrictions, indentations and budding forms were common and gave rise to bizarre pictures. An attempt has been made to illustrate some of these peculiar shapes in figure 6. From the presence of nucleoli, it seems likely that this atypical division was common among the ganglion cell elements.

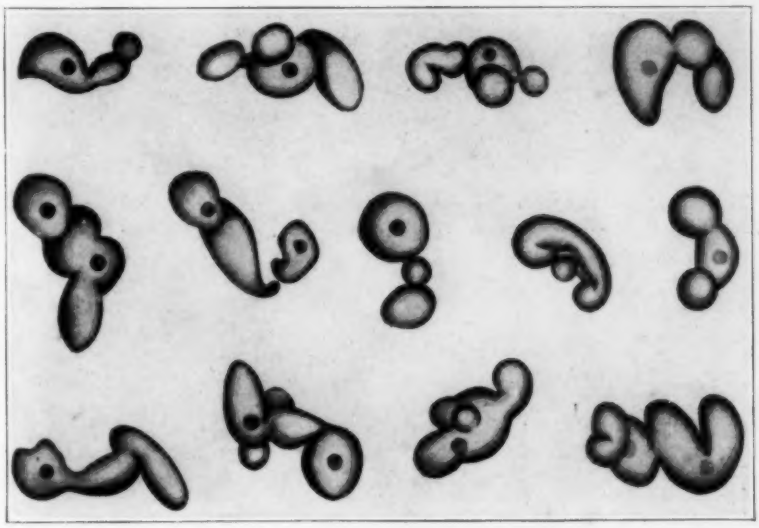

Fig. 6.—Peculiar nuclear forms found in the tumor cells. An attempt has been made to give the impression of three dimensions.

Ganglionic Series.—With the aid of specific methods, the larger tumor cells were identified as belonging to this group. They were of two types: (*a*) bipolar and unipolar cells which composed the larger fibrous strands or (*b*) round or irregular cells which formed clumps of cells between the strands. With the reduced silver method of Cajal the unipolar and bipolar cells in the strands were found to be typical neuroblasts. Some of them were evidently the origin of unmyelinated nerve fibers (fig. 7 *A*). As these cells increased in size the nucleus became more and more vesicular and the processes were more intensely impregnated with the silver. In some parts of the tumor definite masses of unmyelinated nerve fibers were observed (fig. 7 *B*).

With the Bielschowsky-Plein method for Nissl's substance, the cytoplasm of the larger cell forms was found to be finely granular (fig. 8). In some of the cells, larger masses were seen in the periphery of the cells but in no case was the

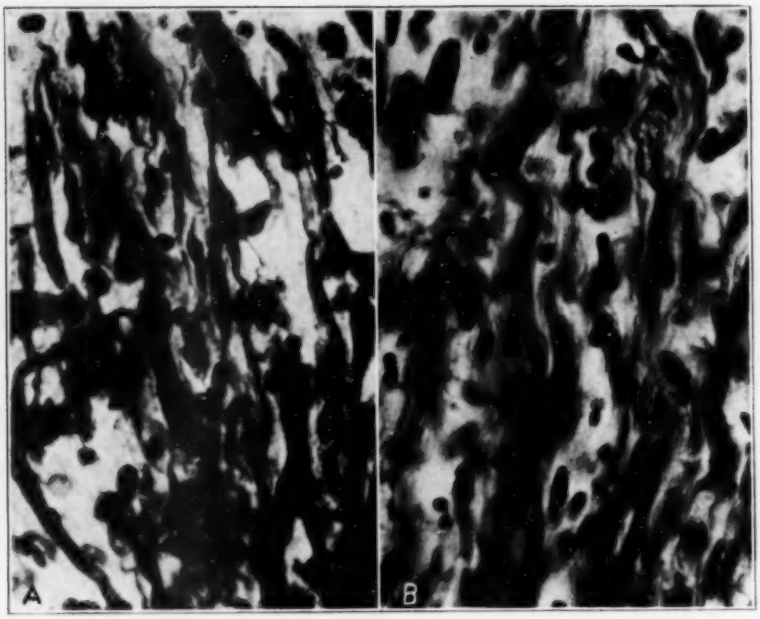

Fig. 7.—*A*, unipolar and bipolar neuroblasts proliferating nerve fibers. Cajal's reduced silver method; × 535. *B*, unmyelinated nerve fibers. Cajal's reduced silver method; × 600.

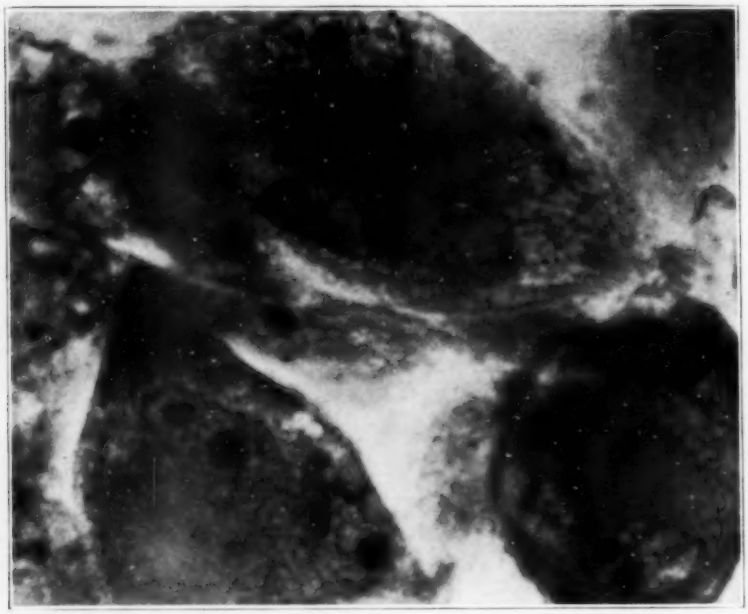

Fig. 8.—Granular appearance of the larger elements, evidently atypical tigroid substance. Bielschowsky-Plein method for Nissl's substance; × 2400.

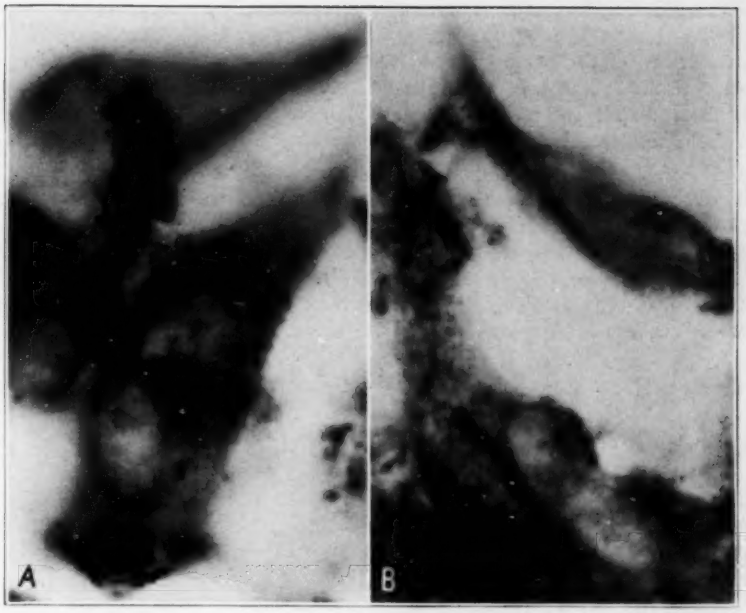

Fig. 9.—*A* and *B*, atypical neurofibrillae in cellular elements. Granules and broken lines are seen in the cytoplasm. Bielschowsky's method for neurofibrillae; × 2200.

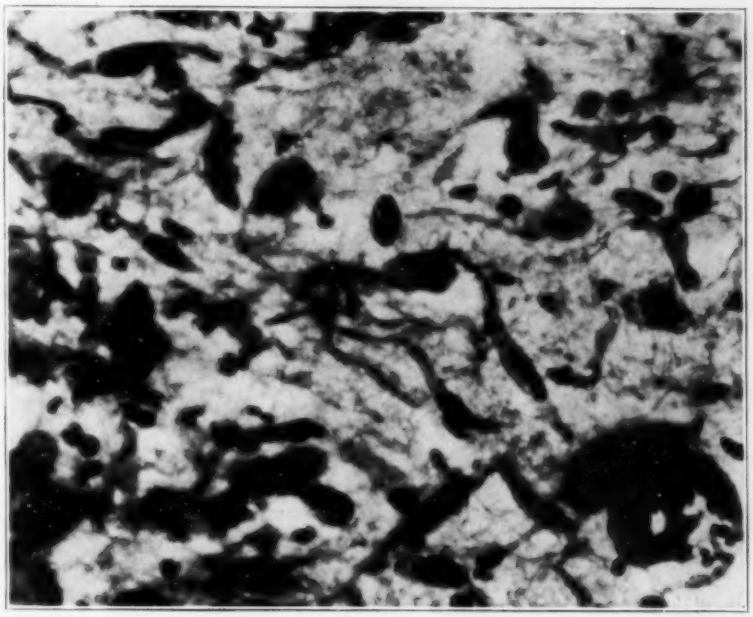

Fig. 10.—Unipolar and bipolar glioblasts (spongioblasts). A mitotic figure is also shown. Hortega's silver carbonate method; × 500.

typical picture of the normal ganglion cell with the closely packed tigroid substance observed. This was due, no doubt, either to the embryonal character of the cell or to the regressive changes which began even before adult proportions had been reached. This is in accord with the observations of other investigators.

Bielschowsky's method for neurofibrillae did not demonstrate these structures as clearly as one would like, although under the higher magnification fibrillary elements could be seen forming the processes of the larger cells and entering into the formation of the fibrous strands (fig. 9). This atypical impregnation may have been due to regressive changes or to the age of the tissue. Even with the imperfections, the impregnated fibers were evidently of nervous structure.

Fig. 11.—Connective tissue about blood vessels forming a "stroma." Perdrau's method for connective tissue; × 95.

Glial Series.—The gold sublimate method demonstrated a glial reaction at the margin of the tumor and occasional monster glia cells within the tumor substance. The immature forms, however, were not clearly shown by this method. The silver carbonate method demonstrated bipolar and unipolar forms, particularly in the tumor margin, and as glial structures in the normal tissue were impregnated the method was considered to be specific (fig. 10).

It would have been more satisfactory if the embryonal cells had been more clearly demonstrated. Careful study with methods revealing nuclear detail demonstrated the presence of typical glia nuclei in which the chromatin was evenly spread throughout its structure. This together with the observation of occasional glia fibrillae as shown by Mallory's method was taken as confirmative evidence of the presence of neuroglial elements.

Vasculature and Connective Tissue Stroma.—From the standpoint of hemorrhage and regressive changes, the ganglioglioma resembles closely the neuroglioblastoma. In either case these observations are due to some effect on the blood vessels which produces solution of the vessel wall, causing a hemorrhage, which results in the formation of a thrombus with occlusion and infarction of the tissue supplied. These reactions may be explained by a toxic effect of the tumor cells on the walls of the vessels, but this is difficult to prove. As the result of degeneration there was an active proliferation of connective tissue which proceeded from the walls of the blood vessels. This was localized as adventitial proliferations or formed extensive, scarlike areas (fig. 11).

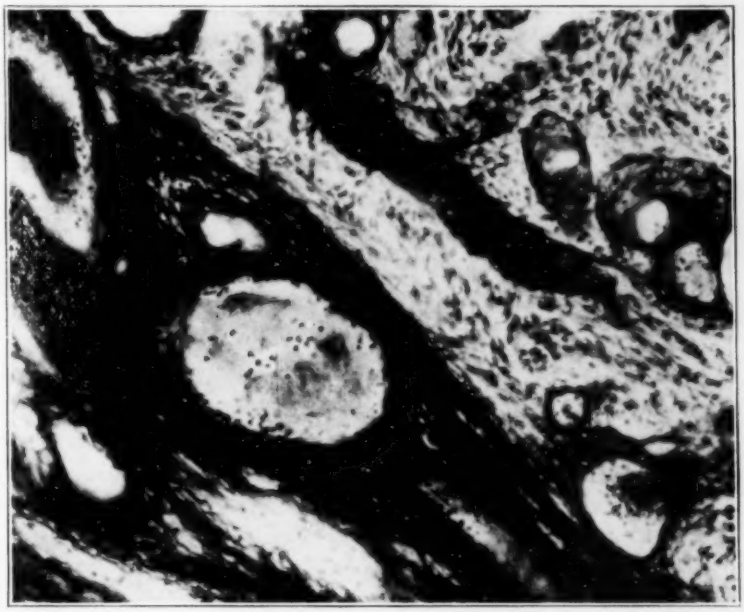

Fig. 12.—Connective tissue about distended blood vessels at the margin of the tumor forms a "capsule." Perdrau's method for connective tissue; × 95.

In the somewhat softened adjacent brain there was an increase in the size and number of the blood vessels. In Perdrau preparations the connective tissue had formed a dense wall about these vessels, making a "capsule" (fig. 12). This was probably not so much a defensive reaction to tumor growth as it was a result of regressive changes in the adjacent softened cerebral substance. In this zone a large number of round cells were observed. They were found also to a less extent within the tumor tissue itself, as has been described by other writers.

The process of phagocytosis of free fat which resulted from extreme regressive changes was very active. The macrophages were found abundantly about the margin of degeneration in closely packed masses. With the combined method of Penfield, the elaboration of phagocytes was traced from bipolar forms to typical compound granular corpuscles. The process seems to have had its starting point in the connective tissue masses about the walls of the blood vessels. Here darkly

staining bipolar cells were seen, which resembled fibroblasts in their simplest aspect. With expansion, the well defined processes were lost and vacuolar spaces filled the cytoplasm of the cell. The scharlach R stain showed these spaces to be globules of fat. Typical microglia were not demonstrated, giving rise to the question as to whether the phagocytes in this case are not of connective tissue origin. If this is true, it strengthens the theory of the "mesenchymal reaction" of the organism to injury as has been described by Maximow.

Comment.—This case of ganglioglioma of the right temporal lobe has all the essential histologic characteristics of the group and furthermore exactly fits the description by other observers of tumors in this situation. Whenever a small, well circumscribed glioma is found in this region at necropsy, it is most likely to be this variety of tumor. One wonders why such a small tumor, located in a "silent" area of the brain and producing practically no local or distant distortion of the cerebral tissues, should bring about the patient's death. Is it possible that the pronounced mental phenomena which are present in the clinical picture in most of these cases as well as their fatal issue in the absence of local serious damage are the result of a toxic product elaborated by the tumors?

RELATIONSHIP OF THE GANGLIOGLIOMAS TO OTHER TUMORS OF THE GLIOMA GROUP

In a review of the stages of neurohistogenesis as encountered in a series of gliomas,[13] it is evident that in most of the embryonal variety neuroblasts as well as glioblasts can be demonstrated by specific methods.[14] If this is true, the gliomas the cells of which undergo differentiation apparently have their cellular origin in bipotential indifferent elements which pass through various stages suggestive of normal histogenesis. This parallel development of glioblastic and neuroblastic elements has been clearly demonstrated in the medulloblastoma by Bailey and Cushing,[15] in the ganglioglioma (gangliogliomeuroma, ganglioneuroma) by several of the German investigators and

13. Courville, Cyril B.: Cell Types in the Gliomas: Their Relationship to Normal Neurohistogenesis, Arch. Path. **10**:649 (Nov.) 1930.

14. The reduced silver method of Cajal is recognized to be of value in the demonstration of neuroblasts in tumors of the glioma group. In order to check the specificity of the method, it has been my custom to take blocks of tissue which included normal brain as well as tumor. Only those sections in which nerve fibers were demonstrated in the normal brain to the exclusion of the glial elements were accepted for study. On only one occasion, in an area of regional gliosis, were neuroglia demonstrated by this method.

15. Bailey, P., and Cushing, H.: Medulloblastoma Cerebelli: A Common Type of Midcerebellar Glioma of Childhood, Arch. Neurol. & Psychiat. **14**:192 (Aug.) 1925.

more recently in the neuroglioblastoma (spongioblastoma) multiforme and the astroblastoma by me. The more primitive types, the medulloepithelioma and the neuro-epithelioma, may also differentiate to the point of neuroblast formation, but I have not been able to verify this by personal study.

In this sense, all of this group of gliomas (perhaps more properly termed "neurogliomas"), with the possible exception of the medulloepithelioma and the neuro-epithelioma, have a more or less common ancestry as far as their cellular elements are concerned. The histologic picture of each type is characterized by the rapidity and degree of cellular differentiation and by the tendency of the constituent elements to assume embryonal arrangements. The picture is altered secondarily by regressive changes incident to a disturbance in the blood supply of the tumor tissue.

Gangliogliomas and "Spongioblastoma Unipolare."—In their contribution to the study of the gliomas, Bailey and Cushing [16] described a slowly growing, often cystic tumor occurring in the early decades of life which they termed a "spongioblastoma unipolare," believing it to be composed largely of unipolar spongioblasts. Under lower magnifications the tissue architecture was seen to resemble closely the peripheral neurinomas. For this reason they were inclined to include the cases of Josephy and MacPherson, described as "neurinoma centrale," with their spongioblastoma unipolare. On the other hand, several of the undoubted cases of gangliogliomas reported, particularly those of Bielschowsky and Henneberg,[17] were also described as having this appearance. The question naturally arises whether or not the individual tumors included in the various appellations are not identical if not closely related.

From the evidence at hand, it seems to be largely a question of the degree of cellular differentiation whether the tumor will be grouped as a "neurinoma centrale" or as a "ganglioneuroma." If many large characteristic ganglion cells and many unmyelinated nerve fibers are found, the tumor is considered to be a "ganglioneuroma." If the cells are less mature and appear largely as unipolar or biopolar elements, the tissue takes on a more fibrous aspect and will more likely be called a "neurinoma centrale." In the last case, careful study will reveal some

16. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis, Philadelphia, J. B. Lippincott Company, 1926, pp. 81, 82 and 139.

17. Bielschowsky, Max, and Henneberg, Richard: Ueber Bau und Histogenese der zentralen Gangliogioneurome, Monatschr. f. Psychiat. u. Neurol. **68**:21, 1928.

unmyelinated nerve fibers as well as glioblasts in addition to neuroblastic elements with vesicular nuclei containing a nucleolus. Cajal's reduced silver method demonstrated that most of these unipolar and bipolar elements are neuroblasts, many of them forming the unmyelinated nerve fibers of the tumor.

Shall all such tumors be termed gangliogliomas? Shall they be included under the noncommittal appellation of the "neurinoma centrale" or shall they be divided into two separate groups? Unfortunately, no single investigator thus far has been able to study enough cases critically to make a final decision. The tumors illustrated by Bailey and Cushing in their monograph would suggest that the "spongioblastoma unipolare" is larger than the ganglioglioma and smaller than the astroblastoma and the neuroglioblastoma (spongioblastoma) multiforme. Together with the facts of slow growth and occurrence at an early age, this would indicate at least that this glioma is out of order in the histogenetic scheme as proposed by these authors. It seems evident that the "spongioblastoma unipolare" should be grouped with more benign forms, probably lying between the astroblastoma and the ganglioglioma, if it is not actually a slightly less differentiated tumor than the latter.[18]

GANGLIOGLIOMAS OF THE TEMPORAL LOBE

As my present records stand, the temporal lobe is second in order of frequency as the location for gangliogliomas. Table 2 gives a list of recognized gangliogliomas in this situation. The temporal lobe is a common location for gliomas of all types, especially the neuroglioblastoma (spongioblastoma, glioblastoma) multiforme which I have come to believe is a closely allied tumor. All of the reported gangliogliomas of the temporal lobe have certain gross characteristics which serve to distinguish them from others of the glioma group. The tumor is usually about the size of a walnut, being much smaller than other gliomas. It is sharply circumscribed, although not encapsulated in the

18. Just before this manuscript was submitted for publication, I studied a large, firm, well delineated glioma of the right temporal lobe measuring about 7 cm. in its greatest diameter, which seemed to answer more nearly the description of a "spongioblastoma unipolare." Parts of the tumor had a characteristic neurinomatous appearance, while in other portions the nuclei of the tumor cells were more suggestive of neuroglioblastoma (spongioblastoma) multiforme. Cajal's reduced silver method showed these fibrous portions to be composed of neuroblastic elements which were proliferating unmyelinated nerve fibers. In other words, this tumor might be considered as a transitional type between a neuroglioblastoma and the "spongioblastoma unipolare." It further strengthens my belief that the latter, as described by Bailey and Cushing, is in reality a tumor tending toward a ganglioglioma in the character of its differentiation.

ordinary sense of the term. Its tissues appear granular and often marked by small hemorrhages. Furthermore, as evidence of its essentially expansive rather than invasive growth, peculiar concentric lines caused by folding and wrinkling of the tissue brain at its margin are often observed.

TABLE 2.—*Reported Cases of Ganglioglioma Occurring in the Temporal Lobe*

Author	Year	Age	Sex	Symptoms	Duration	Gross Pathology
Schmincke (Beitr. z. path. Anat. u. z. allg. Path. **47**: 354 1909-1910)	1910	17	M	Epileptiform convulsions; became idiotic in later years of illness	9 years	Sharply demarcated grayish-white, walnut-sized tumor in anterior part of right temporal lobe
Katzenstein (Inaug. Diss., Wurzburg, 1910)	1910	16(?)	M	Epileptiform convulsions; mental changes (negativism); sexual infantilism; death in coma	More than 10 years	Grayish-white, sharply demarcated, granular tumor about size of a walnut in anterior part of right temporal lobe
Schmincke (Verhandl. d. deutsche path. Gesellsch. **17**: 537, 1914)	1914	17	M	Somnolence and choked disks	?	Sharply demarcated, spherical, walnut-sized, grayish-yellow tumor in anterior part of right temporal lobe
Bielschowsky and Henneberg (Monatschr. & Psychiat. u. Neurol. **68**: 21, 1928): Case 1	1928	16	M	Drowsiness, headache and failing vision with choked disks; right hemiparesis	11 years	Tumor slightly larger than a walnut arising from the roof of the inferior horn of the left lateral ventricle
Case 2	1928	11	F	Marked mental symptoms, convulsions, bilateral deafness, ataxia and vomiting; failing vision with optic atrophy	7 years	Small, grayish-red tumor mass, 2.5 cm. in diameter, in the hippocampal gyrus of right temporal lobe; small metastasis to inferior surface of right cerebellar lobe
Courville	1930	35	F	Marked mental symptoms, headaches and vomiting; blurring of vision with choked disks; left hemiparesis with tremor; possible homonymous hemianopia	9 months	Tumor 2.8 by 2.6 cm. in sectional diameters arising in region of the hippocampus of the right temporal lobe; grayish-red; central degeneration and cyst formation

On careful study it will be observed that the tumor probably has its origin in the region lateral to the hippocampus in the floor, or occasionally in the roof, of the inferior horn of the ventricle. If one accepts tentatively the conception that they are due to the development of misplaced cell "rests," it is possible that they arise from embryonal elements that have deviated from the rather complex development of the

hippocampus and have lodged in the adjacent tissues. Such cells must have originally been bipotential in order to elaborate both glial and ganglionic elements such as are found in the tumor.

SUMMARY AND CONCLUSIONS

A short review of the problem of the nerve cell containing gliomas is made, and a case of a tumor of this type in the right temporal lobe is reported. It fulfilled the essential characteristics of the group, but differed from some in its greater cellularity, the smaller amount of stroma and the presence of mitotic figures. The characteristics of gangliogliomas of the temporal lobe are presented, together with a table of the cases reported. They are similar to in many respects, if not identical with, the "spongioblastoma unipolare" described by Bailey and Cushing.

THE MARCHI METHOD

A DISCUSSION OF SOME SOURCES OF ERROR AND THE VALUE OF THIS METHOD FOR STUDYING PRIMARY CHANGES IN THE MYELIN SHEATH *

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The Marchi method was originally devised for and has been extensively used as a means for working out the finer details of neuroanatomy. Its value for this purpose lies in the fact that it is the most convenient and on the whole the best method for following myelinated nerve fibers which are undergoing active degeneration as a result of accidental or experimental lesions. Although it is generally conceded that the use of the method requires considerable experience, it is the accepted technic on which much of present knowledge of fiber tracts is based.

The method has also been used extensively in studying the histopathology of the nervous system, particularly that of the peripheral nerves. A review of the literature and some original work on this use of the Marchi technic have convinced me that its value for such purposes is limited, and that much confusion has arisen as a result of its indiscriminate application. It is not my purpose to offer destructive and uncalled for criticism of work much of which is undoubtedly good, but rather merely to point out errors that have apparently crept in from time to time owing to uncritical use of the Marchi and allied methods.

MATERIAL AND METHODS

The material studied consisted of portions of the sciatic nerves or brachial plexus from 108 rats, human peripheral nerves obtained at autopsy in 35 different cases and portions of the vagus and splanchnic nerves of 6 dogs, 6 rabbits and 12 cats. The rats included the Wistar strain of albinos, the Long and Evans strain and the wild gray Norways.

The material was examined in teased preparations and in paraffin sections. Staining was done by the regular Marchi method, by the Busch modification of the Marchi method, Mallory's connective tissue stain, hematoxylin-eosin, thionine, toluidine blue, sudan III and scharlach R.

Details of the various methods are discussed in connection with the results obtained. The term Müller's fluid refers to a solution containing 3 parts of potas-

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* From the Department of Anatomy, University of Minnesota.

sium dichromate and 1 part of sodium sulphate in 100 parts of distilled water. Marchi fluid was prepared by mixing 1 volume of 1 per cent osmic acid with 2 volumes of either Müller's fluid or a 3 per cent solution of potassium dichromate. The Busch mixture contains 1 part of osmic acid and 3 parts of sodium iodate in 300 parts of water.

REVIEW OF THE LITERATURE

Before discussing the value of the Marchi method in studying the pathology of the myelinated fibers, it is necessary to give a brief account of the various types of degeneration taking place in these fibers.

First of all there is secondary or wallerian degeneration. The term secondary means the degeneration that follows or is caused by destruction of the contained axis cylinder. The death of the axis cylinder may be brought about either by separating it from its cell of origin, or by the death of that cell. This type of degeneration has been studied extensively and can be demonstrated in fresh tissue as well as in variously stained preparations. It is not in the scope of this paper to discuss the details of this process other than to emphasize that it should always be designated as secondary or wallerian degeneration and not simply as nerve degeneration, degenerative changes or other ambiguous terms.

A second well recognized type of degeneration is the so-called retrograde degeneration. This is a centripetal degeneration caused by extensive crushing or pulling of a nerve. It is always accompanied by violent changes in the cells of origin, and hence is probably due to a disturbance of the cell bodies. According to Ranson (1904), it is usually indistinguishable histologically from strict wallerian degeneration. The chief difference between the two types is that the retrograde type occurs much later after the primary injury than does the degeneration of the peripheral portion.

In addition to the types already mentioned, which are clearly defined and generally accepted phenomena, there are other degenerative processes in the myelin sheaths that may be designated collectively as primary degeneration; that is, degeneration of the myelin sheath which does not necessarily occur as a result of degeneration of the axis cylinder. The literature on this type of degeneration is scattered, and a review of it is rendered additionally difficult because of the various terms that have been applied to it, such as periaxillar degeneration, myelin changes, myelin degeneration, slight degeneration, nerve degeneration and others. However, the following points have been gathered from the literature.

1. In multiple sclerosis there is a true primary degeneration of the myelin sheath. The statement is usually made in textbooks on neuropathology that the axis cylinders may be seen in sclerosed patches from which the myelin has long disappeared. Two of the more recent papers

favor this view, and many instances from the literature supporting this view are stated therein (Leiner, 1922, and Hassin 1923).

2. Globus and Strauss (1922) came to a similar conclusion in regard to subacute combined sclerosis or progressive funicular myelopathy, as it is termed in their paper. They stated definitely that the myelin degeneration precedes that of the axis cylinder.

3. Kernohan and Woltman (1929), in discussing an incisure of the crus cerebri due to a contralateral tumor of the brain, stated that this case furnishes evidence that compression may cause local destruction of the myelin without destroying the axis cylinder or causing descending degeneration.

4. Gombault (1880) described a local destruction of the myelin of peripheral nerves in lead poisoning which was not accompanied by destruction of the axis cylinder. However, the exact nature of the changes in lead poisoning has been disputed up to recent times and Gombault's description cannot be said to be entirely accepted today. (Hyslop and Kraus, 1923).

5. One of the latest papers on the effects of feeding polished rice to birds, that of Cully (1927), gives evidence that in the resulting polyneuritis the degeneration produced is markedly different from wallerian degeneration in that the myelin may be lost entirely while the axis cylinders remain intact.

6. Pappenheimer and his associates (1929) reported a loss of myelin without apparent injury to the axis cylinder in neurolymphomatosis gallinarum, a disease of unknown etiology.

It appears certain, then, that there is sufficient evidence for saying that there is such a thing as primary degeneration of the myelin sheath, i.e., degeneration preceding or not accompanied by destruction of the axis cylinder. Such a process is especially true of certain diseases of the central nervous system, and to a less extent accepted as a type of degeneration in the peripheral nerves. However, Doinikow (1913) and Kimura (1919) both expressed the belief that the axis cylinder may be involved in lesions of the peripheral nerves of all types, and Doinikow expressly stated that the primary changes of peripheral neuritis sooner or later lead to typical wallerian degeneration.

In the instances cited, the actual disappearance of the myelin was demonstrated by the Weigert and other methods. When it can be shown that on one hand the myelin has disappeared from a certain area and on the other that axis cylinders are present in the same area, there seems to be no doubt that one is dealing with a type of nerve degeneration different from the wallerian. However, there are numerous

instances in the literature in which the evidence for a disturbance of the normal conditions is based on less convincing observations. The outstanding example of this is the various interpretations put on results obtained from the Marchi method; in the following pages are cited some of the observations that have been recorded.

Singer and Münzer (1888) found that in most Marchi preparations black particles were to be seen that could have no possible relation to experimental or accidental lesions. They found the same black particles in preparations from entirely normal animals. They said that the particles were to be seen in the myelin sheaths from all parts of the nervous system, both central and peripheral. In cross-sections of the spinal cord, black particles were scattered throughout the entire section with minor differences in number in the various parts of the cord. They were especially numerous at the point of entrance of the anterior rootlets. Singer and Münzer were able to show that black particles could regularly be produced by crushing the myelinated fibers immediately before fixation of the tissue. The black substance produced had only a superficial resemblance to the blackened products of wallerian degeneration. They emphasized their observations as a source of error in interpreting the results obtained by the Marchi method. They recommended that the tissues be kept for at least three months in Müller's fluid instead of eight days as originally called for in the method.

Teuscher (1890) noticed scattered black droplets both in the myelin sheaths and between the fibers in peripheral nerves from cachectic persons. In tuberculosis especially he noted a fine general dotting with little coal-black droplets between the fibers. The droplets had no characteristic situation, and the number of them varied greatly in any one case. Teuscher thought that the black stippling might be a response to the tuberculous cachexia. He also noticed that in some of his sections the axis cylinders were stained black while the myelin remained uncolored. This has been occasionally noted during the present work.

Hammar (1895) remarked that he found scattered black droplets throughout his preparations from frogs, mice and rats. He said that they were never numerous, but never completely absent.

Teljanik (1897) claimed that black particles other than those due to wallerian degeneration could be removed by differentiation by the Lustgarten-Pal method.

Weigert (1897), in a critical review of the Marchi method, said that scattered black particles must not be regarded as evidence of wallerian degeneration, and that their presence must be properly allowed for in all experimental work. He suggested that they might be of considerable pathologic importance.

Elzholz (1898) found that the Marchi method revealed scattered black droplets in the myelin sheaths from the proximal stump of a severed nerve. He described these bodies as staining either brown or black. They were found lying within the myelin, between the myelin sheath and the neurilemma, and in the protoplasm of the sheath cell. While their size varied, they were usually smaller than one-half the diameter of the sheath. The shape of the particles was usually spherical, but was sometimes irregular. In addition to being found in the proximal stump, Elzholz found these bodies or corpuscles in peripheral nerves in cases of multiple neuritis and also in smaller numbers in normal persons. He considered them to be derived from the myelin and classed them under the general heading of metabolic products.

Freund (1899) examined the brachial plexus and the femoral and sciatic nerves in twenty-eight cases of death from gastro-intestinal diseases. He found that the Marchi method did not reveal any characteristic increase in the black granulation. In seventeen of the cases he examined the rootlets and found an increase in seven of them. He believed that this demonstrated a greater resistance on the part of the peripheral nervous system to toxic conditions.

Meyers (1901) said: "It must be added, however, that in certain sections of brain prepared by the Marchi method, black granules very closely resembling the products of degeneration are found at times in the normal nerve and tract (optic). There is in every case, however, a striking difference in the microscopic appearance of the two tracts and the two nerves." Farther on he said that the use of Flemming's fluid will prevent the appearance of these particles.

Spielmeyer (1903) believed that the black granulation observed in the Marchi preparations was due to postmortem handling.

Matuszewski (1905) regarded the Marchi preparations that were not controlled by other methods as unreliable because of varying interpretations placed on the actual observations.

Buzzard (1907) described two distinct types of nerve change in acute toxic conditions: (1) typical wallerian degeneration; this he saw in a case of pneumonia complicated by alcoholic neuritis, and (2) fine droplets scattered throughout the central nervous system and the anterior and posterior roots. These droplets lie within the fibers, seldom fill more than one-half the diameter of the sheath, vary in depth of staining and lie either singly or in short rows of two or three. While Buzzard said that this second type is usually associated with some functional disturbance of the nervous system, he found that such changes were common in a series of eleven fatal toxemias which had no nervous involvement. He said, "The importance of this result lies in the warning it provides that we should not be too ready to regard this diffuse type of myelin change as explanatory of marked functional disturbance in the form of paralysis or loss of sensation."

De Lange (1908) wrote of the necessity of careful control of all observations based on the Marchi method. He concluded that there is no way of entirely eliminating black granules that are not the result of the experimental lesion. He found that formaldehyde must be used with care, but recommended a mixture of equal parts of Müller's fluid and a diluted solution of formaldehyde, U. S. P. (1:10) for the first two days, followed by many changes of Müller's fluid. He believed that the amount of black precipitate or granulation varied directly with the amount of postmortem handling and recommended fixation in situ. He found that black granules were more numerous in young animals than in mature ones and that this was in accordance with previous observations by Spielmeyer and van Gehuchten.

Lewy (1909) emphasized the need of care in interpreting the black particles scattered throughout the preparations. The method he recommended is practically the same as that of De Lange, i. e., formaldehyde for from twenty-four to thirty-six hours followed by many changes of 3 per cent potassium dichromate.

The following passage is found in Allbut and Rolleston's "System of Medicine" (1910):

"The myelin sheaths of the nerve tracts in the spinal cord, and to a less extent those of the peripheral nerves, often present a form of diffuse fatty change when examined by Marchi's method. In longitudinal sections small droplets of fat are seen lying singly or two or three together along or between nerve fibers, and do not fill the transverse area of the myelin sheaths. This appearance may

be found in toxic states unassociated with paralysis, and does not therefore indicate necessarily any functional alteration in the nerve fibers."

Jakob (1912) said that there occur in the spinal cords of normal men myelin balls which are identical with the Elzholz corpuscles of peripheral nerves. They may lie either inside or outside the myelin sheath; they have a great affinity for acid fuschin; they stain brown or black with the Marchi method, and they never give a fat reaction with sudan III or scharlach red. They vary greatly in number and appear to be metabolic products derived from the myelin sheath. He believed that they must be considered in evaluating the results of all work with the Marchi method. Jakob cited Alzheimer as being of the same opinion.

Vedder and Clark (1912) found that in the vagi of polyneuritic fowls stained with Marchi's fluid every fiber from segments 2 to 5 mm. in length showed one or more blackened areas along its course. In none of the fibers was there any vacuolization of the sheath or collection of degenerating myelin into the large globules such as is typical of nerves after section. The amount of blackening in the vagus nerves had no definite relation to the severeness of the disease in the individual birds. Their illustrations lead one to believe that they were dealing with Elzholz' corpuscles. The only mention they made of normal fowls is that in the spinal cords of these an occasional black droplet is seen either within or without the myelin sheath. The illustrations of normal teased preparations are entirely free from black droplets.

Doinikow (1913) found that Elzholz' bodies stain brown, black or gray when the Marchi method is used. He said that they may be divided into two groups: (1) the bodies that lie within the cells of the sheath of Schwann and, (2) those that lie either in the myelin or between it and the neurilemma. The second group of bodies is in general larger than the first type, and they are found lying beside a vacuole when the Marchi preparation is counterstained to bring out the normal myelin. When the quantity of these bodies is not great, they are found in the places designated, but when the number is great they often look like strings of beads at various points in the internodal segments. Doinikow found the bodies widely distributed throughout the animal kingdom; they were seen by him in fish, amphibia, reptiles and mammals. Of the mammals, guinea-pigs, rabbits, cats, dogs, horses, monkeys and men were studied. In these they always occur in varying quantities. Concerning the Elzholz bodies, Doinikow made some significant statements: 1. Their diverse staining reactions are evidence of their varied chemical nature. 2. They are present in normal animals of many species. 3. They stain pathologically with the fat stains in experimental neuritis of rabbits and guinea-pigs. 4. In man there are Elzholz' bodies which normally stain with such fat stains as sudan III and scharlach red. These are usually pin-point droplets in the cytoplasm of the sheath cells, but in the aged they may be large and extend into the myelin itself. 5. The quantity of the Elzholz bodies has no pathologic significance, and their staining reactions do have some such significance.

The impression gathered from Doinikow's paper is that the Elzholz bodies are unreliable as an index of a pathologic condition of the nerves.

Wilson (1913) gave the following description of his results of examining peripheral nerves from cases of pellagra: "By Marchi's method for degenerated myelin it is not very common, except in advanced cases, to find typical Wallerian degeneration, but, on the other hand, there are constant diffuse irregular changes, consisting in small collections of lipoid substances, fragments or flakes of myelin, sometimes small round particles of myelin, either inside the neurolemmal sheath

or in the cells of the endoneurium. It is also common to see degenerated myelin sheaths which have not disintegrated or become discontinuous, but nevertheless stain with osmic acid."

Shimazono (1914) described the Elzholz corpuscles as being round, elongated or irregular, and occasionally ring-shaped. They usually appear near the nodes of Ranvier, according to his observations. The larger corpuscles may cause a bulging in the myelin sheath at the point of their location. Shimazono found that the number of Elzholz' bodies increases in a large number of toxic and nutritional disturbances, and he is definite in his belief that they are of some pathologic significance.

Manalang (1917) examined the vagus and posterior tibial nerves from 110 cases gathered at autopsy. He found more or less degeneration in 88 of these cases. In 4 cases the degeneration was recorded as severe. Ten of the cases were cases of accidental deaths with no other pathologic change. Manalang found degeneration to a moderate degree in 6 of these cases. He made no distinction between wallerian and other types of degeneration. The illustrations given, as well as the results obtained, indicate that he was not dealing with wallerian degeneration, and the illustrations of the nerves appear similar to the pictures described as Elzholz' corpuscles. Manalang was unable to find any relation between the degeneration he found and any single bodily condition. He mentioned that some pathologic change was noted in the kidneys in 67 of the cases, and that a low grade beriberi was apt to be present in the population from which the cases were drawn. The Marchi technic was followed throughout, and nerves were left in the regular Marchi fluid for fifteen days.

Kimura (1919) noted an increase of Elzholz' corpuscles over the normal in pigeons and fowls fed on polished rice. He stated that the corpuscles were present in the normal pigeon he examined, but to a much less extent than in the birds with polyneuritis. Kimura used Flemming's fluid to bring out the Elzholz bodies and found that they could not be stained with the ordinary fat stains. He was impressed with the lack of correspondence between the degenerative pictures obtained and the severity of the disease.

Voegtlin and Lake (1919) said that the most striking changes in experimental polyneuritis of cats and dogs were found in the nervous system. "The teased sciatic nerves of practically all animals which developed symptoms showed myelin degeneration varying from a mild type, characterized by a foamy appearance of the myelin and a swelling of the nodes of Ranvier, to a typical, well marked degenerative process involving many fibers, similar to that seen in pigeons with polyneuritis gallinarum. A few spinal cords studied showed some degenerated fibers at all levels. The amount of change found in the nerves and cord did not always correspond to the severity of the symptoms in the animals."

It must be emphasized that they make no distinction between the various types of degeneration. The illustrations show typical Elzholz' corpuscles in moderate numbers. No mention is made of the occurrence of similar bodies in normal nerves, but fibers from normal animals are illustrated as being entirely free from black particles. Only the Marchi method was mentioned by Voegtlin and Lake in their investigation of the nervous system.

Marui (1919), in a study of two cases of "central neuritis," found "definite" changes in the Marchi preparations, but so scanty as to be incongruous with changes in the nerve cells and axis cylinders. No mention is made of what type of change was observed in the myelin sheaths by use of the method.

McCarrison (1921) clearly recognized a difference between wallerian degeneration and that which he refers to as the "patchy" type. This "patchy" type, the description of which fits that of the Elzholz bodies, was found in normal pigeons as well as in controls. He found some degeneration, mostly slight patchy changes in 88 per cent of the test birds, and the same changes to a less degree in 33 per cent of the controls. In monkeys, such changes were found in nine of thirty-three animals; all nine were test animals. McCarrison was of the opinion that the importance of the degeneration revealed by the Marchi method in polyneuritic animals had been overestimated.

Hamilton and Nixon (1921) said that contrary to the generally expressed opinion, degenerative changes in the peripheral nerves are common in pernicious anemia and constitute an important part of the pathologic anatomy of the disease. They suggested that lesions of the peripheral nerves may explain the disharmony between sensory phenomena and changes found in the spinal cord in certain cases. They demonstrated this degeneration by means of the Marchi method and found varying amounts of degeneration in six of seven cases studied. They said that the Marchi method will reveal degeneration when other methods, including the Weigert, are negative. They did not distinguish between wallerian degeneration and primary degeneration, but their figures compare well with illustrations of the latter type and also with appearances seen in many normal nerves studied here.

Sachs and Alvis (1921), using the Marchi method to follow wallerian degeneration, expressed the opinion that considerable experience was required to interpret the observations by this method. They repeated De Lange's caution as to the necessity of washing out all formaldehyde before the tissue is placed in Marchi's fluid, and in the best preparations degenerating fibers must be followed from one section to another to avoid misinterpretation.

Globus and Strauss (1922), in their paper on subacute combined sclerosis, made the following statement about Elzholz' bodies: "These were found everywhere in large numbers, particularly in areas of acute softening. They occur along the course of naked axis cylinders, between myelin sheaths and the neurilemma, and independent of axis cylinders or myelin sheaths. The lack of uniformity in distribution, the absence of a definite relationship to axis cylinder or myelin sheath leads us to conclude that they cannot be looked on as an indication of primary axis cylinder disease," as claimed by Shimazono.

Hyslop and Kraus (1923) made the following statement in their discussion of the pathologic changes of motor paralysis by lead: "If the Marchi or Weigert stains bring out pathologic changes it is safe to assume their existence."

Wilson and Winkelman (1924), using the Marchi method in two cases of multiple neuritis from carbon monoxide poisoning, found a marked increase in the Elzholz bodies in some of the peripheral nerves examined; in others the changes were less marked; in others they were entirely absent. The nerves were more uniformly involved in the first case than in the second. Axis cylinder stains revealed no abnormality of the cylinders except an occasional slight fusiform swelling of the sheath. The spinal cord was normal.

Allen (1924) mentioned the occurrence of a considerable number of fine black granules in some of his Marchi preparations that could not be accounted for as a result of the experimental procedure.

Riquier (1925) believed that if great caution was used in handling the tissue the results of the Marchi method could be relied on. He found that this method brought out a great increase in the Elzholz corpuscles in the peripheral nerves of pigeons on a polyneuritic diet. At the same time the axis cylinders were normal. Riquier stated that Elzholz' bodies were rare in normal pigeons. He described

the differences between this type of change and wallerian degeneration. He found that the proximal portions of the nerves were affected more often than the distal portions.

Shimazono (1926) said, "Elzholz corpuscles tend to be found all over the nerve fiber centrally as well as peripherally in the normal nerve apparatus." He believed that the corpuscles are an index to the physiologic state of the nerve, that they are increased by beriberi, tetanus, pain and fatigue, and that moderate exercise reduces their number.

Moore and his associates (1927) found extensive myelin degeneration in the nerves of young rats whose mothers were fed an inadequate diet supposedly low in vitamin B. In recovered cases, considerable myelin degeneration was present six weeks after clinical recovery. No distinction was made between wallerian degeneration and other forms.

Woollard (1927) said that handling tissue before fixation will give rise to a positive Marchi reaction, and that injecting a mixture of equal parts of a diluted solution of formaldehyde, U. S. P. (1:10) and 3 per cent dichromate solution before the nerves are removed is essential. Using this method of fixation, he found no significant changes in the nerves of rats on a beriberi diet, or in those that were simply deprived of food. An occasional black droplet was seen in the sciatic nerve, there being greater numbers in the more peripheral portions. Attention is called to the fact that Riquier made exactly the opposite statement regarding the location of the black droplets, i. e., that they were more numerous in the proximal portions of the sciatics of pigeons.

While no attempt has been made to review all papers dealing with the pathologic process of any one form of peripheral neuritis, or to read all papers in which the Marchi method has been used, it is believed that enough instances have been cited to bring out clearly the lack of any generally accepted rules for the interpretation of results obtained from the use of the Marchi method. It is certain that those (Alzheimer, Buzzard, and Doinikow) who have made critical studies of the Marchi preparations are agreed that the results are to be evaluated with caution, much as they differ on certain minor points. On the other hand, several instances have been cited to indicate that even in recent years, results obtained from the Marchi method alone have been regarded as a certain indication of marked pathologic change in the myelin sheaths.

The general impression gathered from original papers and from textbooks on the subject is that peripheral neuritis from a great variety of causes is accompanied by a certain amount of alteration in the myelin sheaths. Although not always designated as such, the changes referred to are usually the presence of Elzholz' bodies revealed by the Marchi stain. Doinikow seems to be the only one who pointed out clearly that when stained by this method, the Elzholz bodies are totally unreliable as an index to any bodily condition. He found that in some instances, contrary to the general rule, these bodies could be stained with sudan III or scharlach red, and when such was the case he regarded the nerve as pathologic.

Buzzard seems to be of the opinion that such bodies occur in toxic states which may or may not be accompanied by appreciable impairment of the nervous system.

Shimazono expressed the opinion that they are the products of fatigue and that, while always present to some extent, there are definite increases in conditions causing fatigue to the nervous system. Among these conditions he lists beriberi, tetanus and overwork.

In the literature on avian and mammalian polyneuritis produced by lack of vitamins of the B group, the same Elzholz bodies have been a source of confusion in the study of the pathologic changes caused by this disease. In the papers on polyneuritis, the Elzholz corpuscles are not referred to by name, except by Kimura and Riquier; nevertheless, there can be no doubt that the black particles described by the others are essentially the same as those described by Elzholz. It is certainly clear that the degeneration in polyneuritis from this source is not of the wallerian type, and this fact has been pointed out repeatedly by Kimura, McCarrison, Riquier and Cully.

On the other hand, I believe that the degenerative appearances that occur in the nerves of healthy animals have been minimized by all but McCarrison. For instance, the illustrations of Voegtlin and Lake show clearly that what they call degeneration is of the primary type, and that the black particles and globules are no more numerous than those that may be found in normal animals. I am of the opinion that the differences found between dogs and cats on diets low in vitamin B, and rats on similar diets are not to be explained as a difference between either the animals or the diets used, but simply as a difference in interpretation of the results obtained from the Marchi technic. Woollard used formaldehyde in fixation of rat nerves, while Voegtlin and Lake, with dogs and cats, said that the Marchi technic was used. This generally means that formaldehyde is not included in the fixing fluid. The differences between formaldehydized tissue and that subjected only to dichromate are in themselves considerable.

There can be little doubt that the black particles and granules described by those who were primarily interested in following wallerian degeneration produced by experimental lesions are the same as the bodies described by Elzholz; and as precipitate and granules they were seen and mentioned several years before the descriptions of Elzholz. In fact, Teuscher, in 1890, suggested their possible relation to the cachexia of advanced tuberculosis.

As was stated in the introduction to this paper, one of the purposes of the work was to determine the cause and meaning of these black particles and if there were ways of controlling them. The literature indi-

cates that on these questions there is no general agreement, so that it is believed that the observations made here may be recorded even though many of them are in accordance with statements found in previous papers.

RESULTS

Before giving a description of the details of the appearance of individual black particles seen in the Marchi preparations, certain general points regarding the entire group must be made clear. First, it should be emphasized that the fibers containing these dark bodies have only

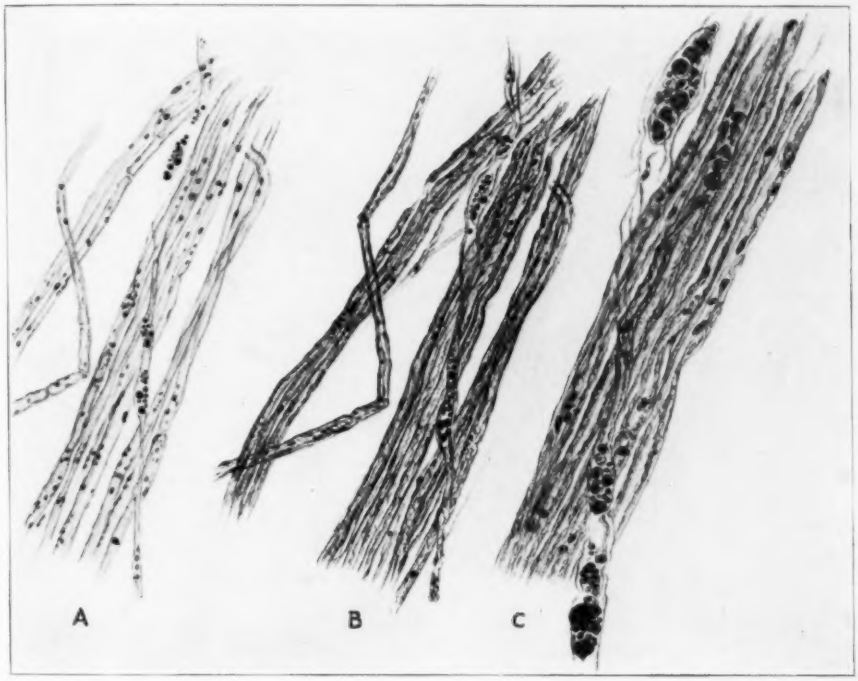

Fig. 1.—Drawings of a fiber in an advanced stage of wallerian degeneration, illustrating the differences between this fiber and the background of normal fibers. All the normal fibers contain black globules or Elzholz bodies. *A* and *B* are drawn at the same magnification, but *B* was drawn with the diaphragm of the microscope nearly closed. With this illumination the solid, unbroken character of the normal sheaths can be seen, while strong illumination is necessary to bring out the black particles shown in *A*. *C*, drawn at a greater magnification, shows the marked differences between wallerian degeneration and the so-called slight or patchy degenerative changes in the myelin sheaths. (From the sciatic nerve of a normal gray rat.)

one resemblance to fibers undergoing wallerian degeneration, and that is the presence of the black coloration. This is well shown by figure 1. The fibers are not broken up into segments and globules as are fibers

undergoing wallerian degeneration, but retain the generally even contour that is seen in all normal fibers. The diameter of the sheath is neither more nor less in areas free from black particles than in those areas that contain them (figs. 2 and 3).

This difference in outline between normal fibers and those undergoing secondary degeneration is well brought out by cutting down the light passing through the diaphragm until the entire field is very dark. Figures 1*A* and 1*B* attempt to illustrate this point. Varying the inten-

Figure 2

Figure 3

Fig. 2.—Drawing of two myelinated fibers from a normal gray rat. These fibers show the maximum degree of black discoloration produced in normal fibers by the Marchi technic. Fibers exhibiting an equally marked pseudodegeneration were seen in nerves from normal specimens of rat, rabbit, cat and man.

Fig. 3.—Drawing of a single fiber from a man, aged 46, who died from a fracture of the skull (case 28-1306). In addition to the scattered black globules, the drawing brings out the foamy appearance of the uncolored myelin, and the axis cylinder is faintly indicated.

sity of illumination also brings out the varying shades of intensity of coloring in the individual particles. With full illumination they all stand out sharply against the yellow background of the uncolored por-

tions of the sheath. As the light is gradually diminished, particle after particle blends with the increasing darkness of the unstained parts of the sheath, until finally when the whole preparation is practically dark only a few of the most densely colored bodies can be made out in the sheath.

Another important fact is that under a low magnification (48 mm. objective) the blackened globules and granules appearing in otherwise normal myelin sheaths are seen as a very fine black stippling or not at all. This appearance of tiny black points and granules is not usually con-

Fig. 4.—Teased preparations from the femoral nerve of a normal rabbit. Black globules and granules, as well as areas of diffuse darkening such as shown in the figure, were to be seen in every myelinated fiber throughout the entire nerve; × 800.

fused with wallerian degeneration even when only a small number of fibers are involved, because the amount of black coloration produced by a very small number of fibers undergoing secondary degeneration and lying close together is much greater than the most intense blackening seen in this series. It is on this account that those who have used the method for the purpose of following bundles of fibers that have been severed from their cells of origin have on the whole paid so little atten-

tion to the numerous fine black particles seen in nearly every Marchi preparation. It is only when very small tracts or isolated degenerating fibers are being studied that the black coloration alone is totally unreliable. In such cases, form and arrangement of the black globules must be taken into account. For example, if the black coloration alone means degeneration, the fibers shown in figures 4 and 5 are certainly degenerated. However, this is not the case; the fibers shown in figure 4 came from a rabbit without discernible abnormality, and those in figure 5 from a splendid specimen from a man who died nine hours after breaking

Fig. 5.—Photomicrograph of typical fibers from the right genitofemoral nerve of a man, age 48, who died of a broken neck; there was no pathologic change (case 28-1295). Illustrations similar to this have been published to show marked degeneration of the myelin sheaths. Paraffin section; × 800.

his neck in a fall. Mallory's connective tissue stain and hematoxylin-eosin revealed no abnormal features in sections from the same nerves.

It should also be mentioned that the black particles or Elzholz' bodies are not particles produced by a diffuse precipitation of reduced osmium compounds, but are always found in intimate relation with the myelin sheaths. In sectioned material they may appear to lie outside the sheath, but teased preparations show that the great bulk of them are either

within the myelin or between it and the neurilemma. Black particles were never seen in the dense fat-free connective tissues (perineurium) surrounding the nerves, nor was any black coloration produced in muscle fibers subjected to the Marchi technic. In sections of the spinal cords from cats with large numbers of the black particles within the white substance, the adjacent gray matter in most cases was entirely free. In only two cases a few of the axis cylinders were stained black (fig. 7).

The shape and size of Elzholz' corpuscles vary greatly within the same fiber. Many of them look like oval or round globules embedded

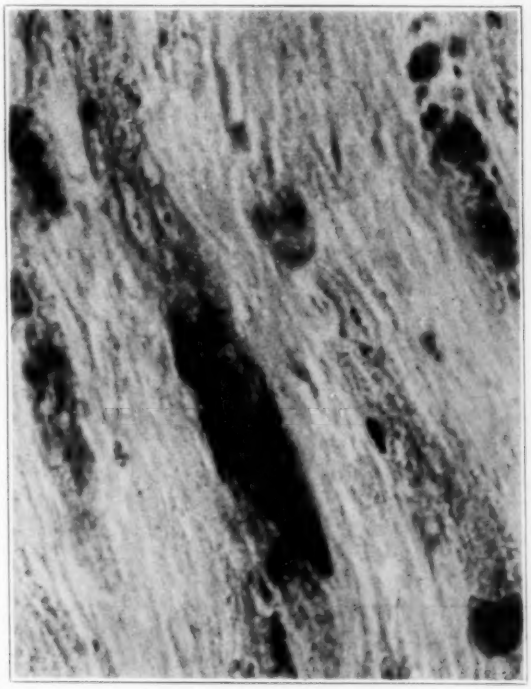

Fig. 6.—A few fibers from the area in figure 5. The large dark spot contains several distinct black globules surrounded by diffusely stained myelin; × 2,400.

in the uncolored myelin, but irregular particles are always seen in the same sheath showing the rounded globules. Figures 2 to 5 show many of the irregular areas composed of fine black granules. In cross-sections of Marchi's preparations of peripheral nerves the irregular areas may be often seen as thin crescent-shaped black lines within the sheath (fig. 8).

The size of the black globules and particles varies from dots that are barely discernible under a 4 mm. objective to droplets the diameter

of which is almost equal to that of the sheath. Droplets large enough to fill the entire diameter of the sheath are rare and the bulk of them are smaller than one-half the diameter of the sheath. The blackened globules vary directly with the size of the fibers, and in very fine fibers they may be fully as numerous as in the larger ones, but their small size renders them inconspicuous in comparison with those in the fibers with a thick myelin sheath.

The Elzholz corpuscles occur singly or in groups. The general location is better shown by the figures than can be described in words. Most of these bodies seem to be within the myelin in teased preparations, although fibers can always be found that show distinctly that some

Fig. 7.—Drawing showing a few fibers from a normal rat stained by the Busch modification of the Marchi method. The fiber at the right is undergoing wallerian degeneration. In two of the normal fibers, the axis cylinders (*Ax.*) have been colored by the osmic acid. Except for occasional small black granules, the normal fibers are stained a clear, even yellow. The general appearance is typical for the entire series of ten nerves treated in exactly the same manner.

are located between the myelin sheath and the neurilemma. This is shown in figure 12. Some black globules were always seen lying entirely outside the fibers in the teased preparations. These globules are thought to have been dislodged in the process of teasing. In sections it is very hard to tell whether the globules are inside or outside the sheath unless they are counterstained with Mallory's connective tissue stain, and when this is done practically all these dark bodies are seen within the sheaths.

When the droplets are seen in groups, they are either clumped together as in figures 6 and 14*B*, or they are laid in rows that bear some resemblance to wallerian degeneration (fig. 9). The groups of droplets are usually separated from similar groups in the same fiber by long intervals of myelin containing no black particles of any kind. Shimazono and others have noted that when the Elzholz corpuscles are present in moderate numbers, they are usually located near the nodes of Ranvier. Although globules in the myelin at the ends of the internodes were seen in every preparation (figs. 9*A*, 10 and 11), this situation was almost exclusively the location of the black granules in only one case. In A-27-1170, a case of ruptured aneurysm of the abdominal

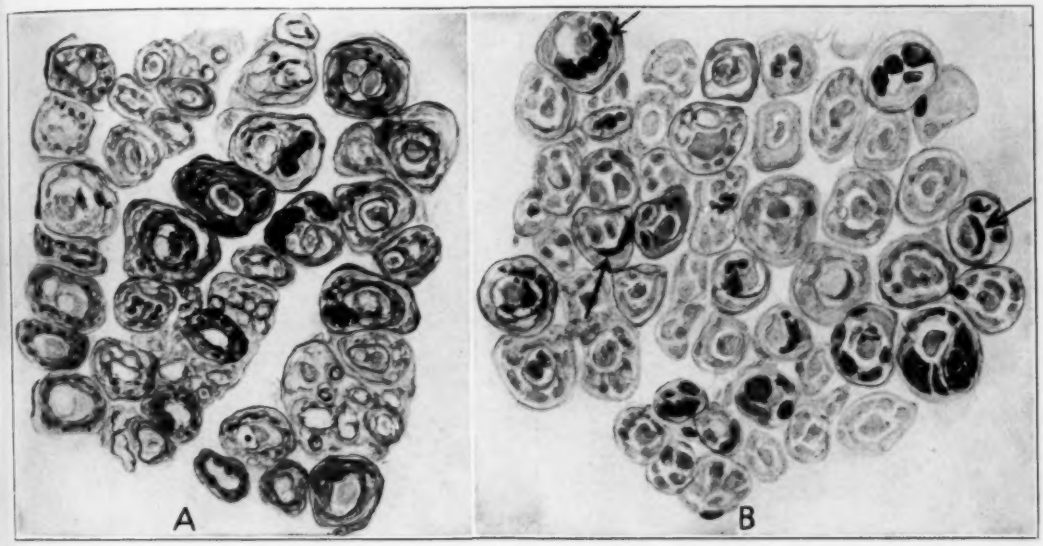

Fig. 8.—*A*, drawing of a cross-section of the left splanchnic nerve of a woman, aged 72, who died from air embolism after thyroidectomy (case A-27-402). Black globules or Elzholz corpuscles are embedded in the myelin sheaths of several of the fibers. Marchi stain. *B*, drawing of cross-section of the sciatic nerve from a normal gray rat. Black globules, as well as irregular black particles, are seen in the sheaths of many of the fibers. Note the crescent or sickle-shaped black areas indicated by arrows. These were seen in all cross-sections studied.

aorta in a man, aged 33, practically every fiber of the right vagus contained a black globule or a darkened area on either side of the nodes of Ranvier, while the remaining portions of the myelin sheaths were practically free from black coloration.

An important fact regarding the position of the Elzholz bodies is that in any preparation all fibers are equally involved; that is, every myelinated fiber contains them somewhere along its course. If the fibers

are examined under the magnification given by a 4 mm. objective, not all fibers contained in a given field will show blackened areas; in fact, many of the fibers in the field will be entirely free and some of them will contain many black globules. But, if any single fiber containing Elzholz' bodies is followed for some distance, long stretches which are free from these particles are always seen, and, on the other hand, if the fibers without black granulation in the original field are followed, areas containing black globules can always be found. This feature has

Figure 9

Figure 10

Fig. 9.—*A*, drawing of fibers from a normal gray rat. Swelling of the sheath accompanied by the presence of large Elzholz globules at the node of Ranvier is illustrated in the fiber at the left. Marchi method. *B*, drawing of fibers from a normal gray rat. This figure, as well as *A*, shows the arrangement of Elzholz bodies in rows, giving an appearance resembling wallerian degeneration.

Fig. 10.—Large myelinated fibers from the left vagus of a dog in which the right vagus was cut ten days before. The areas indicated by arrows are seen as black globules against a straw-colored background when examined under a microscope. Such globules are common in Marchi preparations of normal nerves; × 870.

been studied intensively and in no case have observations been made that would tend to show that only certain of the fibers were involved while others were entirely free.

When subjected to the same technic, no differences were observed in the general appearance of the Elzholz bodies from the various species studied, dog, cat, rabbit, rat and man. It was thought that more irregular flakes and fewer definite globules were present in the nerves from rats than in nerves from the human cases, but the difference was never sufficient to make it possible to distinguish the nerves of one species from those of the other.

Attempts were made to correlate the amount of black coloration in the peripheral nerves with some general condition of the body. The

Fig. 11.—Fibers from the brachial plexus of a normal rat. The animal was perfused with 3 per cent potassium dichromate before the nerves were removed; 3 per cent dichromate, three weeks; 1 per cent osmic acid, ten days.

attempt was unsuccessful, but the following definite statements can be made.

In human nerves some black particles and globules were seen in all nerves examined. In none of the thirty-five cases was there any suggestion in the history or in the autopsy observations to indicate that the nerve examined was involved in any functional disturbance. Nerves from healthy normal persons killed by accident contained as many Elzholz' bodies as those from cases of acute and chronic diseases.

The nerves from healthy, well nourished rats exhibited changes equal to those in rats extremely emaciated and paralyzed from the effects of

feeding on a diet low in vitamin B. No consistent differences were observed in nerves from animals on diets low in vitamins A or E when compared to nerves from healthy rats of the same age.

Fibers from the sciatic nerves of rats deprived of rest until they were practically moribund looked exactly like fibers taken from their controls. Nerves from rats 4 months old exhibited Elzholz' bodies to a degree equal to that seen in rats 20 months of age and equal to that seen in any of the human cases. In very young normal rats, less that 100 Gm. in weight, the number of corpuscles was very small even when the treatment with osmic acid was excessive. Black granulation was seen in nerves of apparently normal cats and rabbits to a degree equal to that seen in nerves from rats and human beings.

While no relationship between the number of Elzholz' corpuscles and anything relating to health or species was established, it was discovered that minor variations in technic produced striking differences in the quantity and shape of these particles. In the following pages are given the results of varying the individual steps in the technic.

1. Flemming (1897) and Riquier (1925) emphasized the effect of sunlight on nerve preparations and recommended that the nerves be kept in the dark from the time of removal until staining has been completed. If the nerves are treated in exactly the same manner, except that while in Müller's fluid or in 3 per cent dichromate some are exposed to direct sunlight for many days and others are kept in the dark, no differences can be detected in the results. This was tested on nerves from cats, rats and human beings. Several times, two pieces of the same nerve were taken; one was kept in the light while in dichromate and the other was kept in a dark closet. After the dichromate treatment, both pieces were placed in the same bottle of Marchi's fluid. When examined, no difference could be detected between the two pieces of the same nerve. In general, nerves containing many black particles may be observed if they are kept in the dark, and preparations practically free from black granulation have been obtained from nerves that have lain for months in bottles of dichromate exposed to direct sunlight. The reverse is also true. In this series of experiments, the solutions containing osmic acid have always been kept in the dark, although Bowen (1928) said that the generally accepted idea that sunlight decomposes solutions of osmic acid is incorrect. It seems to be certain that sunlight has no effect on the results of the Marchi technic up to the point of immersing the nerves in an osmic acid mixture.

2. It is generally conceded (Mallory and Wright, 1913) that the sodium sulphate in Müller's fluid has no known value. No differences were observed between nerves fixed in the regular Müller fluid and those fixed in 3 per cent potassium dichromate.

3. The length of time the nerves are in 3 per cent dichromate or Müller's fluid has little effect on the results obtained. A series of ten human nerves, one of which had been in 3 per cent dichromate for one week, one for six months and others for periods between these two extremes, were placed for eleven days in the same bottle of Marchi's fluid. The quantitative and qualitative picture of the

black particles seen in the sheaths was practically the same in all cases. The uncolored myelin between the black particles was of the same shade.

It should be noted that the foregoing results apply only to small pieces of tissue; larger pieces, such as the whole brains of small animals, must be kept in the dichromate for longer periods to insure complete penetration. Pieces of nerve kept in 3 per cent dichromate for two years became very brittle and dark brown. When they were placed in a mixture of dichromate solution and osmic acid for a few days and then examined, they looked somewhat different from nerves that had been less than six months in dichromate; but the essential picture of varying numbers of black particles and globules within the sheaths was still present. Pieces of small nerves, such as the peroneal of the rat, that have been kept in dichromate for twelve hours and then one hour in 0.5 per cent osmic acid look practically the same as a piece of the nerve which has been in dichromate for three weeks and in Marchi's fluid for ten days. In pieces of small nerves left over night in dichromate and then placed for ten days in 1 per cent osmic acid, the fibers are very dark, but not uniformly black like those which are placed fresh into osmic acid. Cross-sections of such preparations look entirely different from the straight osmic acid preparations and cannot be used for counting the number of fibers.

4. Numerous authors have suggested that rough handling of tissues after death may be the cause of the black particles and globules known as slight degenerative changes, Elzholz' bodies, etc. De Lange claimed that he had direct evidence that such was the case. In order to test this point the right and the left sciatic nerves from 21 rats were examined. In these cases the entire right thigh was fixed with the nerve in place, while the left nerve was jerked out of the animal with the fingers. In those cases in which the technic was otherwise uniform no differences were found between the two nerves. In order to be more certain that there were no slight differences not discernible by mere observation, counts of the number of black particles were made for each nerve. This was done by examining the teased preparations under the ordinary high dry power lenses (4 mm. objective). The slide was moved slowly across the stage, and whenever a fiber which passed straight across and through the center of the field was seen, the number of black spots were counted in this fiber. The counts were made for 100 such fibers in each preparation. The sums of these counts for pairs of sciatic nerves were as follows: right 50, left 38; right 30, left 15; right 256, left 282; right 88, left 86. The two members of a pair were in the same dichromate solution and the same Marchi fluid, but each pair was in a different solution from the other pairs. Other counts were made on pairs of nerves in which the right nerve was in a different Marchi solution from the left. In these cases there was no correspondence between the number of particles, and the effects of pulling and handling could not be measured. Crushing the nerves, on the other hand, does cause the production of large amounts of a black precipitate to form on either side of the point of pressure. This was pointed out by Singer and Muntzer long ago (1888). From the observations cited, I am certain that ordinary handling of the nerves will not produce an appreciable difference in the results obtained from the Marchi technic.

5. Immediate fixation of the tissue, preferably by injection of the fixative before the nerves are removed, is considered an essential point by Woollard. This seems to be a reasonable precaution because of so many known instances in which immediate fixation is essential for good microscopic preparations. On the contrary, the results from this study indicate that it makes little difference whether the nerves are fixed immediately or twenty-four hours post mortem. Four rats

were perfused with 3 per cent dichromate, and the results obtained from them were no different from those with other rats of the same series in which two hours elapsed after death before the nerves were placed in the fixative. In the human cases, the length of time between death and autopsy had no perceivable effect. Manalang arrived at the same conclusion on this question.

6. It was thought that the use of ether might be a possible influence on the results of the Marchi method. The fact that the same globules and particles were found in rats that were decapitated as in those that were killed with ether, and that in the one human case in which the patient died under ether showed no noticeable differences from other human nerves would appear to eliminate the question as to the possible effects of ether.

7. No differences were observed between teased preparations and ordinary paraffin sections.

8. As previously noted by De Lange and independently by Sachs and Alvis, certain precautions are necessary if formaldehyde is used in the Marchi technic. It was found that if formaldehyde is used it produces great alterations in the results obtained from the Marchi technic. It is believed that many of the contradictory results obtained by various observers are due to the use of formaldehyde. In the first place formaldehyde alters the general structure of the myelin sheath, especially in its production of wide clefts of Schmidt-Lantermann. This point has been thoroughly discussed by Bito.

If formaldehyde is used in fixation and is not completely washed out before the Marchi fluid is used, pictures of pseudodegeneration are regularly produced (figs. 12, 13 and 14 *A*). On the other hand, if the tissue is fixed for twenty-four hours in a neutral diluted solution of formaldehyde, U. S. P. (1:10) washed in running water for twenty-four hours, and then dichromated, the number and size of the black particles are regularly reduced (fig. 14 *B*). The effect is so marked that results obtained from the use of formaldehyde cannot be compared with those in which only dichromate is used.

9. Certain other modifications of the Marchi technic were tried in an attempt to eliminate all black except that due to wallerian degeneration. Of these methods the only one that is satisfactory is that of Busch (Lee: The Microtomists' Vade-Mecum, 1928, p. 598). In this method the tissue is fixed for twenty-four hours in a diluted solution of formaldehyde, U. S. P. (1:10), washed for twenty-four hours in running water and then placed in a mixture containing 1 part osmic acid and 3 parts sodium iodate in 300 parts distilled water. Pieces of spinal cord or peripheral nerves left in this mixture for five days are almost entirely free from scattered black particles and those that are present are of pin-point size under high dry power (4 mm. objective). In contrast to this, fibers undergoing typical wallerian degeneration stand out sharply as rows of jet black globules and segments of blackened myelin (fig. 7). These preparations were the nearest approach obtained to a specific stain for wallerian degeneration. Tissue left for one week in formaldehyde does not give as good results because of the numerous black flakes and granules present. Thorough washing of the tissue after formaldehyde fixation is as essential in the Busch modification as in the regular Marchi method.

Nerve tissue stained directly with 1 per cent osmic acid and then placed in a dilute solution of hydrogen peroxide can be made to look exactly like Marchi preparations. Likewise, the proper exposure of a Marchi preparation with a heavy pseudodegeneration to hydrogen dioxide will take out all black material but some of the black globules of fibers in wallerian degeneration. While this

work is interesting and some good preparations can be produced, it is not regarded as the best routine method, because the action is very rapid. A matter of a few seconds makes so much difference that no two persons would obtain the same results.

Fresh nerves were placed in hydrogen peroxide for twenty-four hours and then stained with osmic acid. Although there was a considerable quantity of gas evolved as the result of the first procedure, the myelin sheaths were stained black as in ordinary osmic acid preparations.

10. Drying the nerves either before or after fixation has a definite effect on the Marchi preparations. If a nerve is laid on blotting paper for from ten to fifteen minutes and then stained with Marchi's fluid, it will be found that the

Figure 12

Figure 13

Fig. 12.—Drawing of fibers from the right genitofemoral nerve from a case of carcinoma of the esophagus in a man, aged 45; cachexia in this case was extreme, and numerous fibers exhibiting typical wallerian degeneration were present in the nerves examined. Compare this figure with figures 13 and 14 *A*.

Fig. 13.—Fibers from the right genitofemoral nerve of a man, aged 40; death was due to gunshot wounds and active tuberculous lesions in both lungs (case A-28-1346). Six weeks in 3 per cent potassium dichromate and ten days in Marchi's fluid. The fibers shown in figures 12, 14 *A* and this figure were in the same Marchi solution, and this solution was contaminated by a trace of formaldehyde carried in with one of the nerves which was from an embalmed body.

myelin of all fibers is filled with a black-staining network. The appearance suggests a deposition of the reduced osmium on the neurokeratin network. The appearance is entirely different from that seen in other Marchi's preparations and, therefore, is not a source of error in the other results reported here.

11. The one major point in the Marchi technic or any modification of it is the use of osmic acid. This is, of course, obvious, but it is believed that the really great differences that can be produced by extremely small changes in the amount of osmic acid used have been largely overlooked or underestimated.

It was assumed when work on this subject was started that if the normal myelin has been dichromated it will show no black particles within its substance even if varying times of exposure and varying concentrations of osmic acid are used; and, further, that as long as some osmic acid is present it will turn the degeneration products of the myelin black. This is decidedly not the case, and may be illustrated by several examples. A piece of a sciatic nerve from a normal rat was placed in 25 cc. of a fresh solution containing one part of 1 per cent

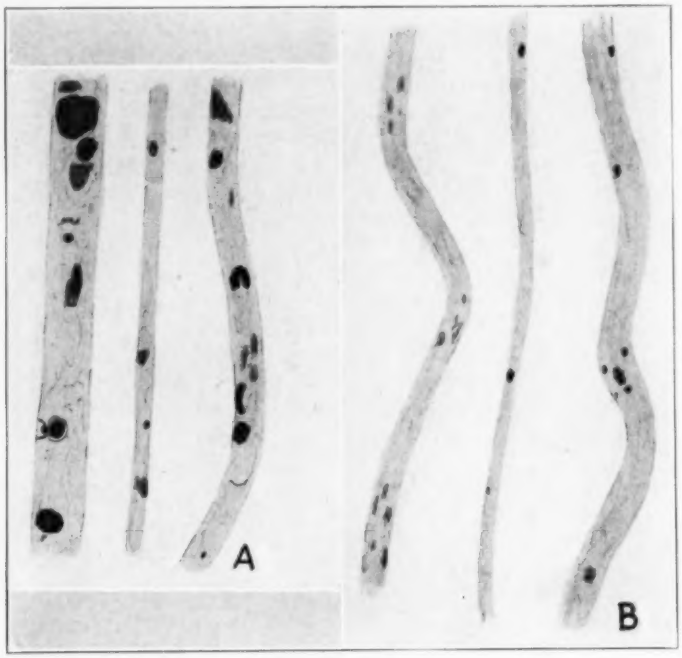

Fig. 14.—*A*, sample fibers from the right genitofemoral nerve of a man, aged 70; death was accidental; no pathologic condition was present (case 28-1609). The fibers shown were placed directly from 3 per cent dichromate containing a trace of formaldehyde into Marchi's fluid for ten days. *B*, fibers from the same nerve as those shown in *A*. The treatment was identical except that the fibers were washed in running water for twenty-four hours before being placed in Marchi's fluid. Note the decrease in the number of black granules due to the removal of the formaldehyde.

osmic acid to two parts of 3 per cent potassium dichromate. This piece remained in the solution for ten days; it was then removed, washed in running water and teased out in glycerin. Every fiber contained black flakes and globules scattered along its course. Several other nerves from diverse sources were placed in the same solution and when examined they all had fewer of the particles than the

first nerve. A piece of the first nerve was now placed in the same old solution (that had been used twice before) and remained there for ten days; when examined a few scattered black particles were seen in the myelin sheaths, but so few in comparison with the first piece examined that one would never have suspected that the two pieces were from the same nerve. Finally, a bit of fat was dropped into the solution, and it turned black in less than an hour, showing that osmic acid was still present in this old solution.

Ten human nerves that had been in dichromate for one week or longer were sewed on a card, and this was placed in 50 cc. of a freshly made up solution of Marchi's fluid containing 0.3 per cent of osmic acid. Five human nerves were similarly placed in another bottle of the same solution. The series of ten nerves remained in the osmic acid mixture for eleven days; the series of five nerves remained in the mixture for five days. The nerves of the first series all presented practically the same appearance. In each case black granules, globules and flecks were seen in every fiber. Those of the second series were likewise all similar to each other but totally unlike any in the first series, because in the latter group black particles were much less numerous. Finally, a series of dichromated nerves made up of three of the first group and three of the second group were thoroughly washed in running water and placed in the Busch mixture. In this group each individual preparation looked practically alike, and the number of black particles present in this case was so few as to make the whole third series different from the second series.

The first twelve nerves obtained from human autopsy cases were treated in the following manner: They were placed in Müller's fluid immediately on removal from the body. The fluid was changed daily for one week, then once each week for two more weeks. At the end of the third week, varying amounts of 1 per cent osmic acid were added to each bottle containing a nerve. The amount added was never more than one-third the total volume of liquid and never less than 2 cc. The pieces of nerves were all of about the same size, and the total volume of nerve tissue was considerably less than 1 cc. in every case. When examined, great differences in the number, size and arrangement of the black particles were noted. The picture produced had no relation to any known condition. Large numbers were found in a man, aged 20, a perfect specimen, who died of fracture of the skull, and a few scattered bodies were found in a man, aged 68, who died of carbon monoxide poisoning and who gave abundant evidence of having chronic alcoholism. In every case the nerve remained in the osmic acid mixture not less than ten days or more than fourteen days, and sufficient osmic acid was always present to give a distinct odor and to color all adhering fat a jet black. Such results seem to support one conclusion, that the exact strength of the osmic acid solution and the length of time the tissue is exposed to the solution must be carefully controlled if any sound facts are to be elicited from a study of the Elzholz corpuscles. This naturally involves another factor which is also difficult to control and that is that in order to be certain of the validity of results obtained from different series of the same technic, the amount of tissue must bear a nearly constant relation to the amount of fluid used. In the latter part of the work this was done by always using a great excess of the fluid, i. e., the tissue making up less than 1 per cent of the total volume.

The experiences with rat nerves were the same as those with human nerves. It was thought that if Elzholz' bodies were increased by toxic conditions, this increase could be demonstrated in animals on a diet low in vitamin B and especially in animals on a diet low in vitamin A, which is accompanied by a high

incidence of infection in the nasal and middle ear cavities. No such increase was observed, nor could any qualitative difference be made out, except that the particles seen in the rats on a diet low in vitamin A looked a little smaller than those in normal animals. This was not sufficiently notable to be stressed in any way. The nerves of rats on a diet low in vitamin B, those on a diet low in vitamin A and their controls were treated in twelve series; each series contained nerves from both the control and test groups, and all the nerves of any given series were placed in the same Marchi solution for the same length of time. The Marchi fluid always contained 0.3 per cent or less of osmic acid, and varying amounts of the fluid were used in each series. While there was considerable difference between individual nerves of the same series, the differences from one series to another were greater than those between individual members of the same series. In each series enough osmic acid was present to color all adhering fat and to color the free fat globules in fibers in advanced stages of wallerian degeneration.

The right sciatic nerve of control rat 2777 was divided into three portions, and each portion was placed in a separate mixture of 3 per cent dichromate and 1 per cent osmic acid that had been used once before. Counts of the number of black particles and globules were made in the manner previously mentioned. The counts were 73, 334 and 716, indicating great differences in the number of Elzholz' bodies present in the different preparations. The differences were evident from direct observation. Recently, Bowen (1928) pointed out the marked effects of minute changes in the strength of the osmic acid solution and its manner of application in staining the Golgi apparatus. While much weaker solutions are used in the Marchi method than in the technic for the Golgi apparatus, the present work suggests that the precautions of Bowen are equally applicable to the staining of Elholz' bodies with osmic acid.

12. The use of other stains revealed no differences between nerves with large numbers of Elholz' bodies and those which were practically free. Attempts to stain the particles with the fat stains, sudan III and scharlach red were unsuccessful.

SUMMARY

Several definite points have been brought out by the present study of the Marchi method. The first is that in any series of Marchi preparations the normal fibers always contain some black globules and irregular areas. For this reason the Marchi stain cannot be said to be specific for wallerian degeneration, although it is sufficiently accurate to be of great value in following the results of this type of degeneration.

The size and number of black areas in the normal myelin have been shown to vary with the fixing fluid used and with the strength of the osmic acid and the time the tissue is exposed to its action. These facts alone suggest that extreme care must be taken in the technic if the black spots other than those of wallerian degeneration are to be used as an indication of pathologic change in the myelin sheath. When, added to this, degenerative pictures equal to those described in pathologic conditions are seen in normal specimens, it seems necessary to say that the pathologic changes described in nerves stained by the Marchi method

should be disregarded unless it is specifically stated that wallerian degeneration was seen. I have determined that as few as 1 fiber of 100 in wallerian degeneration is a marked departure from the normal, and therefore of more significance than any number of black droplets and granules scattered along an unbroken myelin sheath of uniform diameter.

CONCLUSIONS

1. Black globules and granules (Elzholz' bodies) in numbers equal to those described by many authors as evidences of a pathologic process have been seen in the myelin sheaths of normal specimens of cat, rabbit, rat and man.

2. The number, size and general appearance of these bodies vary greatly with very slight modifications of the Marchi technic.

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SOME HISTOLOGIC FEATURES OF THE CRANIAL NERVES*

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In a previous contribution,[1] some mention was made of the fact that, histologically, the eighth cranial or acoustic nerve was composed of two different portions or segments. These have been described before and were accurately named by Henschen,[2] in 1915, as the glial and non-glial portions of the nerve. The fact that glial tissue extends into the cranial nerve trunks has been noted by other observers from time to time in the case of one or the other of the cranial nerves, although very little detailed information concerning this peculiar glial outspread appears to be available in the literature. The object of the present study has been to investigate the cranial nerves from this standpoint.

With this general motive in mind, four principal objectives were outlined: (1) the determination of the amount of glial outspread into the various nerve trunks; (2) the determination of the types of glia cells to be found in the glial portion of the nerve; (3) the disposition, function and relation to the nerve fiber of the glia cells in the glial portion, and (4) the nature of the junction between the glial portion and the peripheral portion of the nerve.

The investigation of these points has now proceeded to a stage where it is possible to report on the observations.

METHOD OF INVESTIGATION

The results to be reported here have been obtained almost entirely from observations made on longitudinal sections of human cranial nerve trunks. Cross-sections of the nerves have been made from time to time and one or two illustrations of these have been included. The majority of the illustrations, however, have been taken from longitudinally cut sections, that is, parallel to the long axis of the nerve.

As much as possible of this work has been done on human material. Confirmatory and experimental work has been done on dog, cat and rabbit material, but almost all of the sections reproduced here were made from human material. The nerve tissues were obtained from selected autopsies, the first requisite being that the subject had been dead not longer than four hours. Whenever possible

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the material was obtained within two hours after death. That this fresh material was available is due entirely to the cooperation of the various pathology services of the several hospitals of London, Ont.

In obtaining the nerve specimens the nerves were divided as far from their superficial origin as possible at the time of removing the brain. This proved to be satisfactory in all cases except that of the eighth cranial nerve where the glial outspread often reaches as far as the internal auditory meatus. In most cases one can obtain a sufficient length of this nerve by cutting it as far as possible within the meatus with a suitable pair of small scissors. To be sure of obtaining good specimens, however, it is advisable to remove the superior wall of the canal with bone forceps and thus obtain a longer portion of the nerve.

The brain having been removed, the attached nerves were then dealt with individually. In removing each nerve trunk from the brain, a small piece of brain tissue was removed along with the nerve in order not to disturb the relations at the point of superficial origin. Usually this attached piece of brain stem, or whatever part it happened to be, was about the size of a small green pea. A fine thread was then tied as close as possible to the peripheral end of the severed trunk and the preparation suspended by the thread in the fixing solution, the attached piece of brain tissue acting as a weight to keep the nerve trunk straight.

In removing the nerves from the brain, great care had to be taken in order that the nerve remained attached to the bit of brain tissue. These two easily become separated for two reasons: (1) Because the fibers of the nerve often pursue a compact course within the brain substance and will pull out of the latter, once they have been divided, as easily as a knife will pull out of a pat of soft butter. This is especially true when there is any degree of softening of the brain tissues. (2) Because the glial portion of the nerve is softer and more easily torn than the peripheral portion. The question has been put to me as to where a cranial nerve would tear if pulled on. This question refers particularly to the point of rupture of the sensory fibers of the trigeminal when avulsed surgically. My experience is that the rupture occurs at the superficial origin of the nerve. I have never yet cut a section of a human cranial nerve in which there has been any evidence of rupture along the line of junction between glial and nonglial portions which could be related to manipulation in removing the specimen.

On the other hand, I have frequently had the misfortune to separate various nerves from the brain, and in these cases the line of separation appears to be at the line of the superficial origin. At the same time it should be stated that when the sections have been cut it is easy to separate the glial from the nonglial portion, although this separation does not always closely follow the line of junction. In connection with this point it is interesting to note that another observer in this department, C. G. Smith, has observed that in pigeons the fifth nerve separates cleanly along the line of junction, leaving the glial dome behind attached to the brain. My own experience with the fifth nerve in man is just the opposite, very light traction on it being sufficient to pull it off the brain at the point of superficial origin.

The fixation fluid most commonly used has been the formaldehyde-bromide solution used by Cajal and del Rio Hortega. This prepares the nerves for the gold sublimate and silver carbonate methods without preventing the use of other methods. Occasionally other fixatives have been employed, e. g., Zenker's fluid. Some experimental variations of the formaldehyde-bromide solution have been tried. These include variations in strength of solution and variations in the hypnotic used. Little improvement in results has been obtained, the original solution still being in use without variation.

Staining methods have, with few exceptions, followed the technic already established. This applies to the ordinary methods, such as van Gieson's hematoxylin and eosin, and Mallory's. It was found necessary to modify Cajal's gold sublimate method [3] on account of the difficulty encountered in getting astrocytes in the nerve trunk to take up sufficient salt to demonstrate their structure. Some improvement was obtained by a variation of this method. This change consists of a variation in the method of immersion of the sections in the gold sublimate solution. The solution was maintained at a higher temperature than the method calls for. The temperature adopted here was from 30 to 35 C. In this method a heavy deposit of gold salt occurs, so that the sections become very dark, the amount of deposition being proportional to the temperature and the amount of time in the solution. It was found that these heavily impregnated sections could be cleared again by immersion in a strong acid solution. Aqua regia was used for this purpose. This solution removes the salt from the background of the section more quickly than from the astrocytes, which are more tenacious of the gold, and results in their standing out clearly on a paler background.

This method was found to be convenient from the standpoint of time as the sections could be left in the gold sublimate solution until it was convenient to deal with them. The length of time most often used for immersion here was from fifteen to twenty hours, which allowed one to carry the treatment of the sections from one day to the next irrespective of the time when the sections were cut. The details of this variation were worked out by W. F. Maguire, technician in the department. It is not suggested that this method gives improved results over the ordinary method. It is recommended for use under two circumstances: (1) when it is inconvenient to deal with the sections from the time standpoint, and (2) when for some reason it is difficult to stain the astrocytes distinctly. The second reason was the cause of adopting this variation, the astrocytes in the nerve trunk being difficult to stain well.

Silver carbonate staining of oligodendroglia was carried out more or less according to Penfield's modification of del Rio Hortega's method.[4] Here the time elements often proved troublesome, but no satisfactory method of obtaining results other than by careful and constant attention to each step is yet apparent.

Other methods have been experimented with, but no satisfactory or illuminating results have yet been obtained by their use. Osmic acid preparations have been particularly disappointing up to the present.

Sections for gold and silver methods were cut by the freezing microtome along the length of the nerve. In every case a control consisting of a piece of cerebral tissue was carried through the same procedure. For other methods the ordinary paraffin technic was employed.

THE LENGTH OF THE GLIAL OUTSPREAD INTO THE CRANIAL NERVES

Extremely accurate determinations of the length of the glial outspread are not possible. The glial tissue ends in a slightly irregular dome formation which makes accurate measurement difficult. The angle

3. Ramon y Cajal: Trab. d. lab. de invest. biol. Univ. de Madrid **11**:219 and 255, 1913; 1916, vol. 14.

4. Penfield, Wilder: Oligodendroglia and Its Relation to Classical Neuroglia, Brain **47**:430, 1924.

which the nerve trunk forms with the plane of its superficial origin also affects the measurement. The actual figures given, therefore, can be considered only as an approximation, although the margin of error has been minimized by averaging the figures obtained by measurement of different sections of the same nerve and by measurement of different nerves.

In any case the figures show such striking differences that small discrepancies in the actual figures cannot affect the results. In order to compare the main observations quickly, the accompanying diagram (fig. 1) has been prepared. This shows some facts which may be summarized as follows: 1. The glial outgrowth into the sensory nerves is more extensive than that into the motor nerves. 2. The glial outgrowth is less marked as one proceeds from the anterior end of the brain toward the spinal cord.

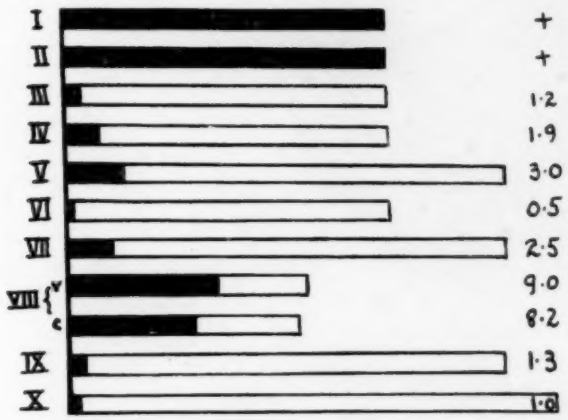

Fig. 1.—Diagram to show the extent of glial spread into the various cranial nerve trunks. The glial parts are represented in black, the peripheral nerve parts in white. The figures give the length of the glial part in millimeters.

The olfactory and optic nerves are represented as being entirely glial in nature. As far as I have been able to discover, no neural crest elements have ever been described in connection with the olfactory nerve. The tract is undoubtedly glial with respect to its sheath cells, up to and including the olfactory bulb. Whether the central fibers of the olfactory nerve cells which pass through the cribriform plate of the ethmoid have a sheath or not I do not know, but if there is any ensheathment of these fibers I should expect it to be composed of glial cells. This would be most unusual, as one would hardly expect to find glial tissue so far afield. Therefore, one must conclude that the branches to the olfactory bulb from the olfactory mucosa are naked fibers so far as sheath cells are concerned.

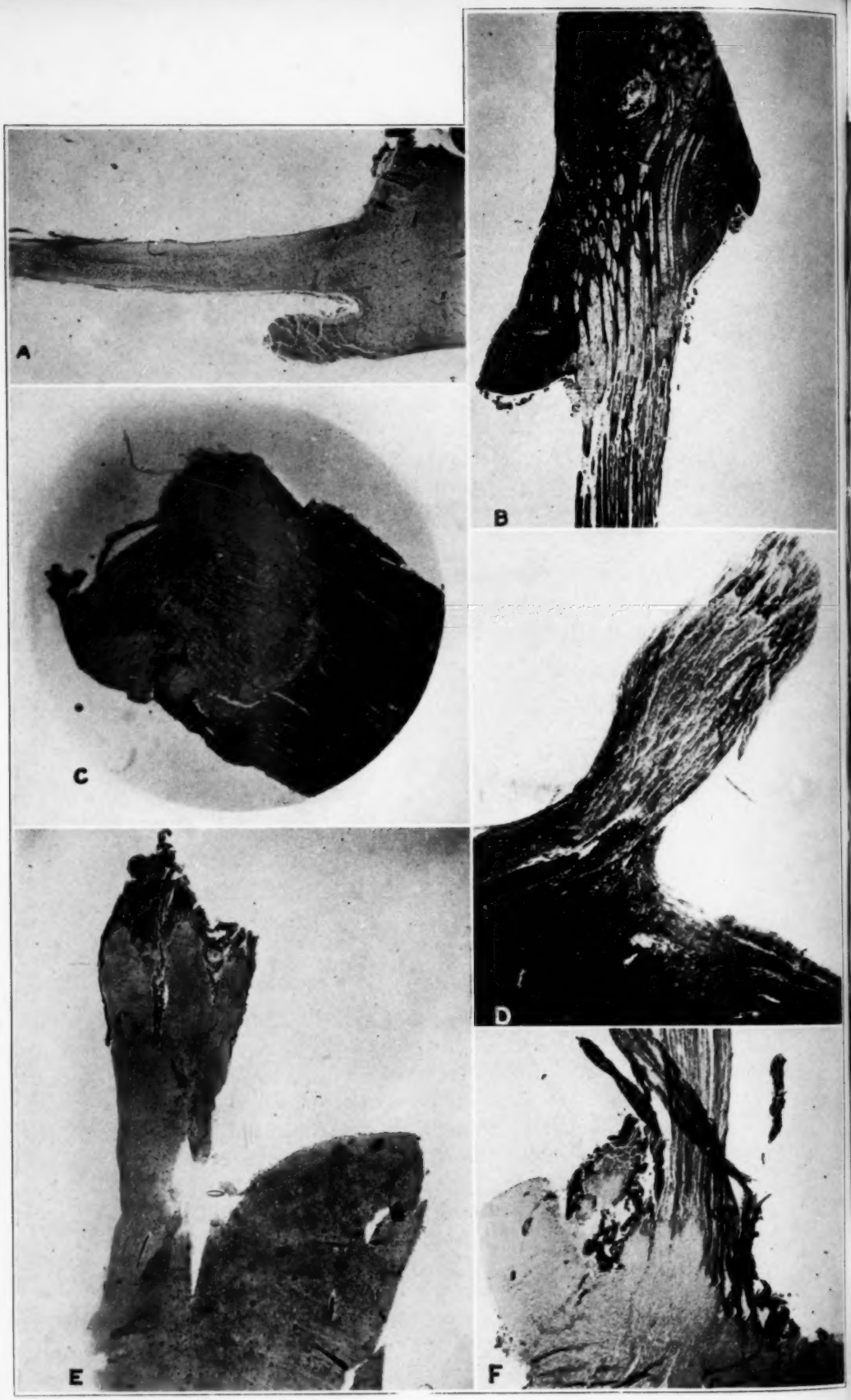

Fig. 2.—Sections of the cranial nerves, showing the form of the glial outspread and its extent in the following nerves: *A*, olfactory tract; *B*, oculomotor nerve; *C*, trigeminal nerve; *D*, facial nerve; *E*, auditory nerve, and *F*, glossopharyngeal nerve.

The optic nerve is glial in its sheath cells throughout, and this is only to be expected from the origin and development of this nerve.

Of the purely sensory nerves, the fifth shows a considerable glial bud, while the eighth contains glia as far peripheral as the internal auditory meatus, reaching a distance, in my preparations, of almost a centimeter from its superficial origin.

The longest glial outspread noted in a motor nerve occurred in the seventh cranial nerve where the glial dome extended as far as 2.6 mm. from the plane of superficial origin. This figure, it should be noted, is less than the lowest measurement obtained in a pure sensory nerve.

The reason for the difference between the motor and sensory nerves appears to lie in certain factors concerned in the development of the nerves. Assuming that an idea already enunciated [1] is correct and that no ensheathing of a nerve fiber takes place until the fiber's connections are established and it becomes, as it were, a live wire or a functioning fiber, I may venture an explanation of these observations.

This may be stated as follows: If the sensory fibers, arising from outlying ganglionic masses, complete their central connections before the motor fibers, growing outward from the central system, complete their peripheral connections, then ensheathment will begin earlier on the sensory fibers.

Are there any facts which support the assumption that sensory fibers may become completely connected earlier than motor fibers? In the case of the eighth nerve, which shows the greatest outgrowth of glia of any nerve that also shows peripheral sheath cells, one sees that the nerve cells of the ganglia associated with the nerve remain in the bipolar state throughout life. In other words, differentiation of these cells does not have to proceed so far as in similar cells of other nerves, or, one might say, these cells are ready to become functional sooner than the sensory cells of other cranial nerves.

A factor of a similar kind can be observed regarding ensheathment. This factor concerns the period at which the ensheathing cells may be ready to take up their function. If the ensheathing elements derived from the neural crest cells (neurilemma [5]) are somewhat slower in developing than the glia cells of the central system, it is possible that the sensory fibers, having completed their central connections and thus formed a bridge along which glia cells might extend, become ensheathed with glial tissue commencing at the central end. This process would continue until the outgrowing glia reached the neural crest elements, the neurilemma cells. At this point, progress in either direction would be halted. Thus in some cases the neurilemma sheath would fail to reach

5. Harrison, R. G.: Further Experiments on the Development of Peripheral Nerves, Am. J. Anat. **5**:121, 1906.

the point where one would expect the line of junction to be, i.e., the plane of superficial origin of the nerve.

The following are factors which it is suggested affect the outgrowth of glia on the nerves.

1. Once a nerve fiber completes its connections and commences to take on the rôle of a functioning unit, it creates a stimulus which tends to produce an ensheathing reaction around it.

2. All of the cranial nerve fibers do not develop at the same time, some fibers and some nerves appearing at an earlier date than others.

3. The glia cells of the central nervous system are differentiated to a point where they are prepared to take on a functional rôle as sheath cells at an earlier date than that of the differentiation of the neurilemma cells to the same point.

The only alternative to some such explanation as that given would be to presume that the peripheral elements (neurilemma) do reach the plane of the superficial origin at some time in the course of development and then cease to extend centrally and progress only peripherally from that time on. With the growth and extension of the nerve fibers it might be supposed that a certain amount of recession of the sheath elements might occur, to be followed by an outward growth of glia. This would, however, result in an outward growth of glia in each nerve proportional to the subsequent growth of the nerve. That this is most decidedly not the case is evidenced by the condition in the auditory nerve, which is the shortest of all and yet exhibits the greatest amount of glial outspread.

Other observers have also noted that the glial outgrowth may vary on the two sides of the same individual, a further indication of embryologic variation.

CELL TYPES OBSERVED IN THE GLIAL PORTION OF THE NERVE

With ordinary staining methods, such as hematoxylin and eosin, one can easily determine the extent of the glial spread into the nerve. Figures *2B* and *2F* show preparations stained by van Gieson's method. The glial portions are clearly indicated.

In the glial portion of the nerve one can distinguish, with ordinary methods, two different types of nuclei. The more numerous nuclei are small, dark-staining and round. The other type is larger and more irregular in outline (fig. 3). Investigation of the nature of these nuclei required the use of gold and silver impregnations.

The actual demonstration of the cell types by means of the gold and silver methods proved to be somewhat difficult. Eventually a fair amount of success was achieved, sufficient at least to identify the cells and observe some facts regarding their distribution.

Two varieties of neuroglia have been identified in the glial portion of the nerve trunk, the astrocyte and the oligodendroglia cell. Microglia has never been observed in a nerve trunk.

The astrocytes are all of the fibrillary type. The cells are not particularly numerous, but each cell appears to give rise to a number of long fibers. These fibers appear most plentifully along the nerve fibers, but can also be observed winding transversely among the adjacent nerve fibers and binding them together. This transverse arrangement is best observed in cross-sections. The glia fiber also tends to take a spiral course as it parallels the nerve fiber.

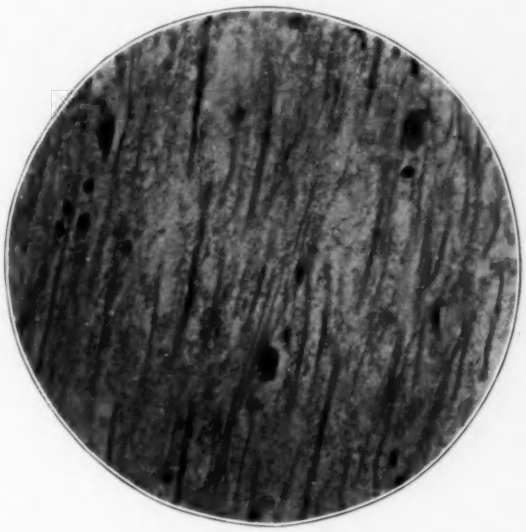

Fig. 3.—Section of the glial portion of the oculomotor nerve, showing two types of nuclei. Van Gieson stain; high power.

A peculiar feature with regard to the astrocytes is related to the vascular conditions in the nerve trunks. Most nerves are very poorly supplied with blood vessels, certainly as compared with brain tissue. In many sections no sign of a blood vessel is evident. For this reason it is impossible to demonstrate the familiar processes of the astrocytes attached to blood vessels, the so-called "sucker feet." One comes to the conclusion that only a very small number of the astrocytic processes are attached to blood vessels. The remainder appear to be glued onto the fibers of adjacent astrocytes, thus forming a real and continuous network.

The staining of astrocytes, as has already been observed, is not satisfactory, particularly in the small nerves. The small size of the nerve

sections and the dangers involved in fixation and treatment of the sections make the correct staining a matter of great care.

The illustrations here reproduced are the best that have been obtained after many attempts. The actual sections show considerably more than can be reproduced in a photograph, as the uneven cutting of the frozen sections and the uneven arrangement of the astrocytes and fibers make it difficult to focus very much of the detail sharply.

The best staining results were obtained in the optic nerve. There seems to be no reason to suppose that the results obtained here should indicate a different condition than that obtaining in other nerves. The neuroglia cells extend longitudinally between the fibers and should

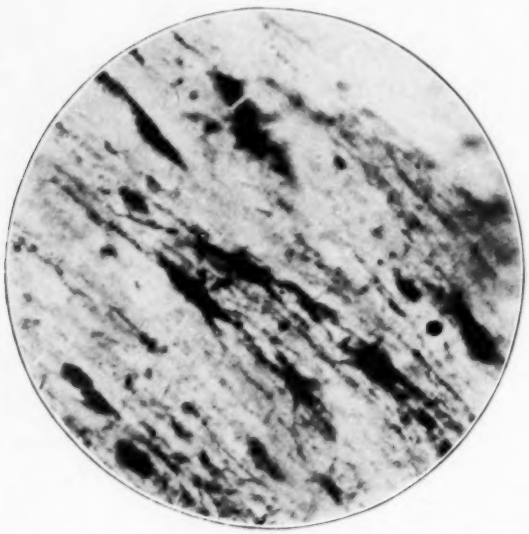

Fig. 4.—Glial portion of the trigeminal nerve. Gold sublimate method to show astrocytes.

represent the typical characters of glia growing longitudinally along nerve fibers. The only difference between the conditions here and that in other nerves is that these glia cells never come up against the peripheral cells (neurilemma, etc.).

In the optic nerve one observes the glia cells arranged in rows parallel to the fibers. It is presumed that they divide so as to progress in this direction. That they follow the nerve fibers and are not laid down according to any other plan is evidenced by the fact that they follow the decussating fibers of the optic chiasm.

If one admits that these cells grow and progress by a series of divisions along the nerve fiber, one can understand how the daughter cell

may remain attached to the parent cell, thus forming the fibrous net already referred to. Secondary attachments to adjacent fibers may occur later as the processes develop and spiral the nerve fiber. Such attachments of fibers are not astonishing when one recalls the connective tissue mesh of the peripheral nerve and its sticky mucinous nature.[6]

The general disposition of the oligodendroglia suggests that it follows the same method of growth and development. Division along a line at right angles to the nerve fiber produces a row of cells parallel to the fiber. This assumption is borne out by the arrangement of these cells in the nerve. In young subjects one frequently notices pairs of

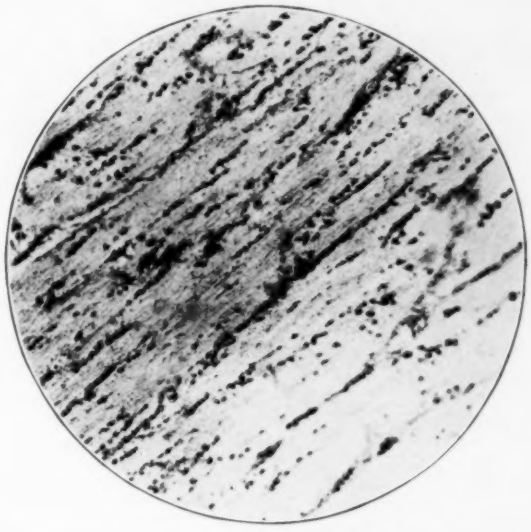

Fig. 5.—Optic nerve; gold sublimate method. Low power view to show arrangement of astrocytes.

oligodendroglia cells so arranged as to bear out this idea. Such a pair may be observed in one of the accompanying photographs (*6C*).

The question of the relation of the oligodendroglia cell to the nerve fiber is one that has aroused considerable interest. There seems to be an increasingly prevailing opinion that the function of the oligodendroglia cell in the central nervous system is exactly similar to that of the neurilemma sheath cell in the peripheral nerve. In fact some authors claim that they are the same cell, and that no distinction should be made between them.

6. De Rényi, George S.: The Structure of Cells in Tissues as Revealed by Microdissection, J. Comp. Neurol. **47**:405, 1929.

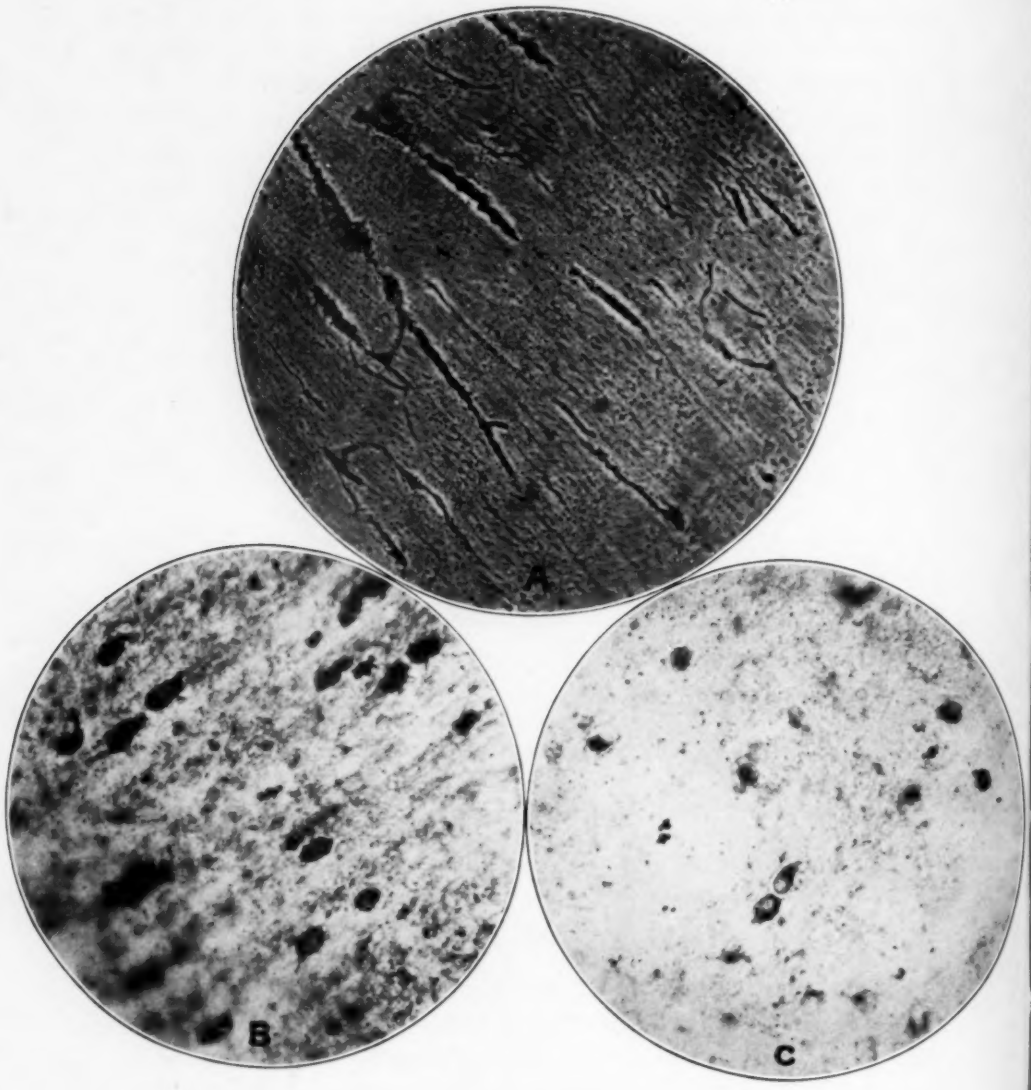

Fig. 6.—The optic nerve, showing oligodendroglia. *A*, low power view to show the general arrangement in rows; *B* and *C*, high power views of longitudinal sections to show the identity of the cells and the tendency to a paired arrangement.

In a recent article, del Rio Hortega stated: "We are now in possession of sufficient arguments to state that the oligodendroglia is absolutely homologous in the encephalo-medullary centres with the Schwann cells of the nerves." This author goes on to say that: "Functionally the expansions of oligodendroglia form involved plexuses which surround (for insulation and protection) nerve cells and nerve fibres, support the nerve tubes in a Schwannoid manner, and their protoplasm elaborates a specific product, which influences the nerve fibres in a trophic way and elaborates myelin." [7]

I am inclined to agree with the latter statement. With the view that oligodendroglia and neurilemma cells are one and the same, I cannot altogether agree. There is no doubt that these two cells occupy the same relative position to the nerve fibers and that in many ways they are functionally alike, but their staining reactions and minute morphology are quite different. Furthermore, in regard to function, an example of a striking difference in this respect is afforded by the action of neurilemma cells following section of a nerve. The regenerative activity displayed by them has never been noted within the central nervous system, nor is any such function accorded to oligodendroglia.

That the oligodendroglia cells are concerned with myelination is indicated by the striking difference in the number of these cells occurring in gray matter and in white matter. This is well shown in the accompanying photographs (fig. 7) and also by the functional activity displayed by oligodendroglia during the period of myelination in embryonic and young animal tissue.[7]

All the available evidence appears to indicate a connection between myelination and the occurrence of oligodendroglia cells. The exact nature of the oligodendroglia protoplasm and processes is difficult to determine. The photographs published by del Rio Hortega show fine processes associated with these nuclei, but just how these processes are disposed with relation to the nerve fiber is not exactly clear.

The most acceptable proposition appears to be an arrangement of oligodendroglia fibers parallel to the nerve fiber with cross branches running around the fiber in a circular or spiral fashion. In the sections presented one sees an indication of such an arrangement in the finely penciled lines running between and across the nerve fibers. But it has not so far been possible to link these fine lines to the oligodendroglia cells.

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7. del Rio Hortega, P.: Third Contribution to the Knowledge of the Morphology and Functional Interpretation of Oligodendroglia, Mem. r. Soc. españ. de hist. nat., 1928, vol. 14, mem. I.

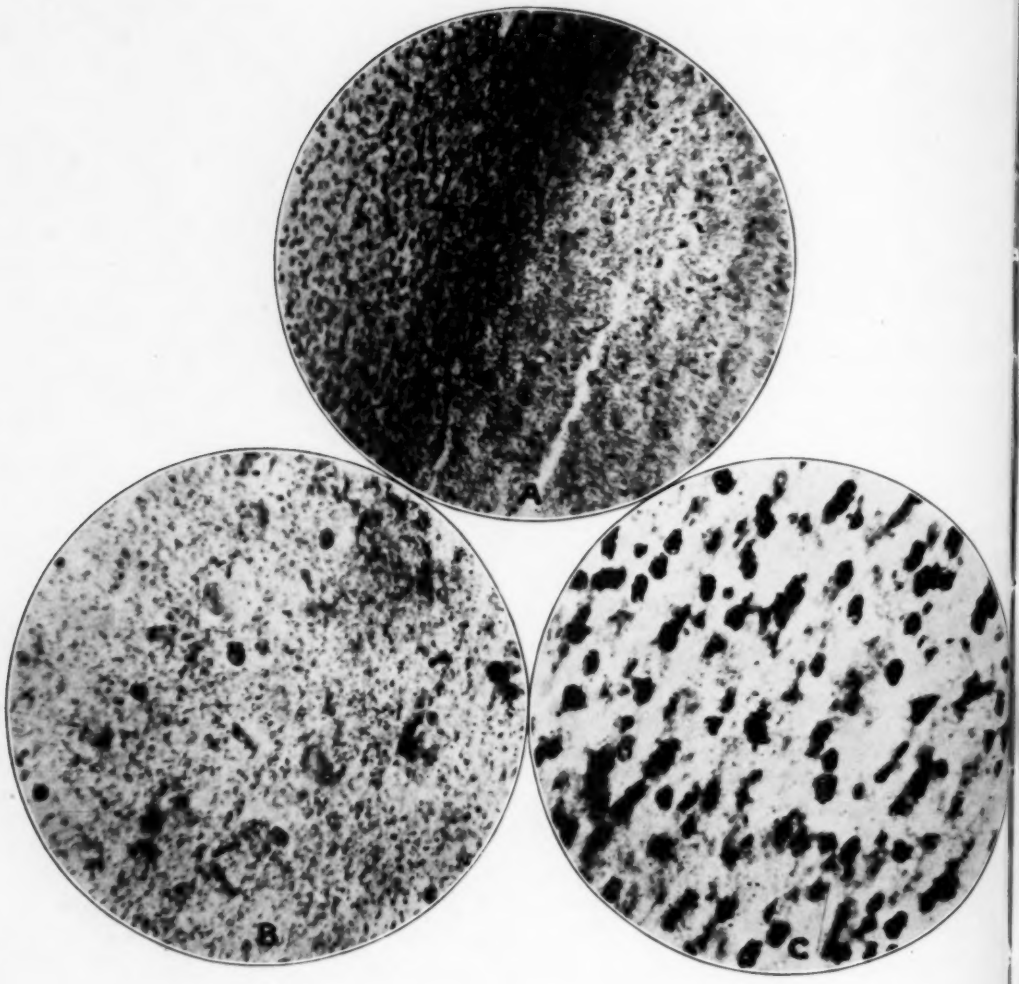

Fig. 7.—Section of the cerebrum to illustrate the distribution of oligodendroglia. *A*, low power view, showing the different appearance of the gray and the white matter; *B*, gray matter; *C*, white matter. *B* and *C* were taken under high power.

Whether these fine processes ever intrude on the myelin in something similar to the incisures of Lantermann is not apparent. One thing appears to be obvious, since there are no nodes of Ranvier in the glial area, the oligodendroglia can have no definite point of meeting with the adjacent cells of the same type, but all must contribute to a general and continuous network of protoplasm which interlaces and embraces the nerve fibers of the white matter.

Fig. 8.—The relative positions of ensheathing elements. *A*, cross-section of the trigeminal nerve to show the position of the astrocytes and their fibers among the nerve fibers; *B*, composite diagram of the ensheathing elements.

It might be stated that, in general, the arrangement of supporting cells within the central nervous system appears to follow the same lines as that in the peripheral nerve. The outer, more fibrous covering of astrocytes takes the place of the endoneurium of the peripheral nerve, and the inner, closer layer of oligodendroglia occupies a position similar to that occupied by the neurilemma.

Two diagrams (fig. 8) are included here to illustrate the arrangement of cells in relation to the nerve fiber. The first is a drawing made from a gold sublimate preparation of the trigeminal nerve, cross-section. It shows how the processes of the astrocytes wind in and out among the nerve fibers, closely embracing them.

The second diagram is a composite representation of the cells concerned in the ensheathing of a nerve fiber. The relationships of neurilemma and connective tissue (endoneurium) in the peripheral segment are compared with those of oligodendroglia and astrocytes in the glial segment.

Of oligodendroglia and astrocytes it might further be said that the oligodendroglia is most concerned with a segment of one fiber while the astrocyte is concerned with binding together many fibers. Oligodendroglia encloses myelin; astrocytes bind fibers together.

NATURE OF THE JUNCTION BETWEEN THE GLIAL AND THE NONGLIAL PORTIONS

In the human being, the line of junction always takes the form of a dome. This dome occurs with every bundle of fibers that can be demonstrated. If the nerve is in several bundles at the point of its superficial origin, then each bundle will show a dome of its own, e. g., oculomotor nerve. If the nerve occurs as one large bundle, the glial dome will extend completely across from side to side, e. g., trigeminal and facial.

Under a low power lens, the line of junction appears sharp and distinct. Under higher power lenses it is not quite so sharp, there being a slight tendency for an interlacing fringe of connective tissue to extend into the glial portion. It is suggested that this circumstance may tend to strengthen the line of junction.

One of the first observations to be made when this region is examined under the microscope is that there is an increase in the number of nuclei present in the glial portion just at the point of junction. On closer examination by all methods, it is found that these nuclei are nearly all oligodendroglia.

In figure 9, the section taken from the auditory nerve shows the condensation of nuclei. The other illustrations, taken from the trigeminal nerve, show the identity of these nuclei and their arrangement. This is particularly a tendency to pile up in files of two, three, four or even more. The suggestion is that an outward movement of these cells has been checked at this point by the oligodendroglia coming into contact with, and being checked by, the neurilemma cells.

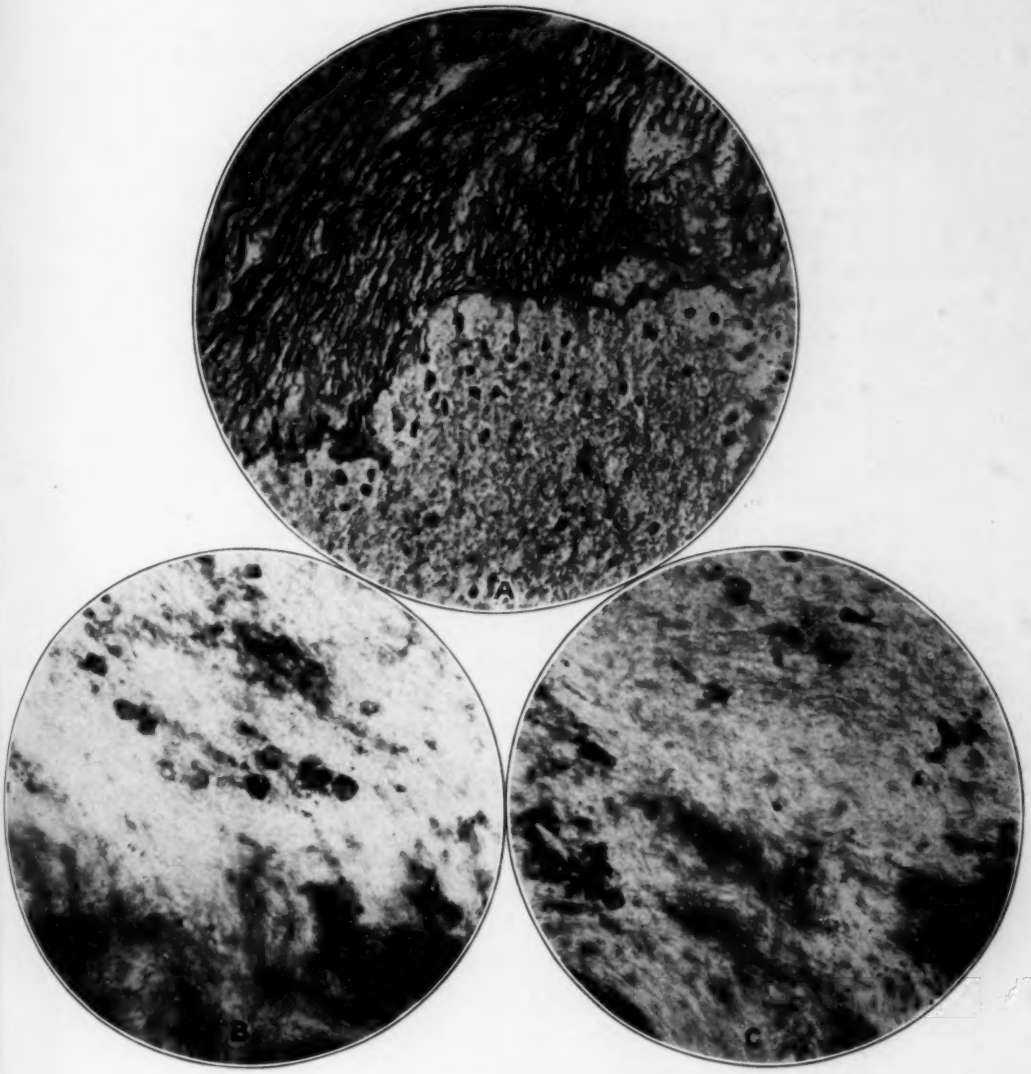

Fig. 9.—The occurrence of oligodendroglia at the line of junction. *A*, high power view of auditory nerve to show the well marked line of junction and the accumulation of nuclei on the glial side. *B* and *C*, two oil-immersion pictures of the trigeminal nerve to demonstrate the oligodendroglia cells and their arrangement.

In gold sublimate preparations there is no sign of any piling up of astrocytes at the line of junction. On the contrary, there is a clear area visible on the glial side of the line where no astrocyte nuclei can be observed. It is suggested that the width of this clear, anuclear zone in gold sublimate preparations represents the average length of an astrocyte process. In some preparations there was an indication of a line of astrocyte nuclei just at the margin of this clear zone, the idea being that from here their processes stretched across the clear area, making contact with the connective tissue fibers.

Following the assumption that ensheathing begins when the fiber becomes functional, it is perhaps reasonable to assume that on the glial side the oligodendroglia cells are the most actively interested at first, since one is accepting a connection between oligodendroglia and myelination. If this is so, one can understand the piling up of oligodendroglia cells at the point where the peripheral elements are encountered. The astrocytes, coming after and consolidating the fibers, are satisfied with merely making a contact with the connective tissue cells the sticky mesh of fibers of which, surrounding the nerve fibers, affords good anchorage to the astrocyte processes. Primary and insulating ensheathment by oligodendroglia is thus followed by consolidating and reinforcing ensheathment by astrocytes.

As regards the dome formation itself, no completely satisfactory explanation is yet apparent. It was thought at first that it might be due to some technical variation due to the cutting of the sections in some irregular fashion. This idea, however, was considerably discounted by the fact that the dome always occurs in human material, but in rabbits' nerves the point of junction is observed to be almost a straight line.

SUMMARY AND CONCLUSIONS

1. From the brain there is an outgrowth of glia cells along the cranial nerve trunks.

2. The amount of glial outgrowth varies in different nerves.

3. It is more extensive in the sensory nerve trunks.

4. The glial extension ends in a dome which is convex peripherally.

5. The cells of the glial portion of the nerve trunk are astrocytes and oligodendroglia. No microglia is observed.

Dr. E. A. Linell, of the Department of Anatomy, University of Toronto, assisted in the preparation of this article.

THE SPINAL ARACHNOID

A NOTE ON THE CELLS IN PATHOLOGIC CONDITIONS *

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The cells lining the arachnoid, known as endothelial cells (Häutchenzellen of Key and Retzius [1]) or, as they are called in this country, mesothelial cells (Weed [2]), are of the low, flat type with large, pale, oval nuclei. The intercellular lines are not clearly defined, except by special staining methods (silver nitrate [1]). These cells cover the arachnoid on both sides and are continuous over the trabeculae which connect the pia with the arachnoid, filling up the subarachnoid space. They also form the outer covering of the pia. The subarachnoid space is thus practically a dense sponge (fig. 1) of connective tissue trabeculae, lined throughout by the mesothelial cells. Being in constant contact with the cerebrospinal fluid, the cells probably react in some manner to the physicochemical properties of the cerebrospinal fluid. The cells in their turn must differ according to the type of the lesion, provided one assumes that the fluid originates from the tissue spaces of the brain and spinal cord. Otherwise, as shown by Hassin,[3] it would be hard to explain the differences in the physicochemical properties of the cerebrospinal fluid in various diseases. To ascertain to what extent, if at all, these cells react in various pathologic conditions, the cells of the spinal arachnoid were studied in thirty-five cases.

The cases studied included: tabes, eight; tabetic type of dementia paralytica, one; multiple sclerosis, one; multiple myeloma of the vertebrae, two; myelomalacia, two; subacute combined degeneration of the cord, four; spinal syphilis, including myelitis and syphilitic meningitis,

* Submitted for publication, Dec. 5, 1929.

* From the Division of Neuropathology (Dr. George B. Hassin), Research and Educational Hospitals of the University of Illinois, and the State Psychopathic Institute.

1. Key, Axel; and Retzius, G.: Studien in der Anatomie des Nervensystems und des Bindegewebes, Stockholm, P. A. Norstedt & Söner, 1875.

2. Weed, Louis H.: The Cells of the Arachnoid, Bull. Johns Hopkins Hosp. **31**:343 (Oct.) 1920.

3. Hassin, G. B.: Notes on the Nature and Origin of the Cerebrospinal Fluid, J. Nerv. & Ment. Dis. **59**:113, 1924; Effect of Organic Brain and Spinal Cord Changes on Subarachnoid Space, Choroid Plexus and Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **14**:468 (Oct.) 1925.

five; streptococcus infection, one; tetanus, one; neurinoma, two; uremia, one; normal (including a case of senility), three; Pott's disease, two; carcinoma of the mediastinum, one, and hemiplegia, one.

METHOD OF EXAMINATION

The material studied was taken from spinal cords that had been preserved in a diluted solution of formaldehyde, U. S. P. (1:10). The arachnoid was gently stripped from the pia and clipped with scissors from the various levels and surfaces of the cord and spinal roots. It was stained in toto by various methods. Of these hematoxylin and eosin (staining with either iron or Ehrlich's hematoxylin and counterstaining with eosin, dehydrating in 95 per cent and absolute alcohol, clearing in xylene and mounting in Canada balsam) was found to give the best results. With this method it was possible to demonstrate cell changes in all of the cases studied.

GENERAL OBSERVATIONS

The most common reaction observed in the arachnoid cells was active proliferation and hyperplasia, which were more or less present in all of the cases studied. In contrast, however, to what is seen in arachnoid membranes of normal cords, the increase in the number of the arachnoid cells found in pathologic conditions was most striking. These appeared as a dense collection of nuclei, either diffusely scattered throughout the arachnoid or in the form of clusters or nests. In such areas the borderlines of the individual cells were not discernible. Instead, the cytoplasm was merged into large, irregular, syncytial protoplasmic masses, which were somewhat pale, vacuolated or spongy (fig. 3).

The nuclei were of two kinds: (*a*) the more mature, comprising the majority, were large, oval and pale with fine chromatin granules, and (*b*) the smaller nuclei, interspersed among the larger ones, which were more rounded, with a deeply stained nuclear membrane and coarser chromatin granules.

Active proliferation of the mesothelial cells was best observed in the less densely infiltrated areas, around the posterior spinal roots and in those covering the trabeculae. The flat, pavement-like character of the cells is well shown even by ordinary staining methods (fig. 2). The cytoplasm of the individual cell bodies was, in contrast to that of the cells shown in figure 3, clearly defined and deeply stained and appeared increased in volume. The nuclei were also more rounded, more deeply stained and rich in chromatin granules; at times they had a definite halo around the nucleus. Mitotic figures were a frequent occurrence, especially in the tabetic type of dementia paralytica (fig. 2). They were also seen in neurinoma, traumatic myelomalacia, multiple myeloma, subacute combined degeneration of the cord and streptococcus infection. Those lining the trabeculae were distinctly swollen, and often were found detached and elongated, resembling fibroblasts. Others

resembled macrophages, but it was not always possible to determine whether they were transformed mesothelial cells or hematogenous elements, derived from the pia, especially when free within the meshes.

As mentioned, hyperplasia of the mesothelial cells was a fairly constant observation, with a tendency to the formation of nests or nodules. These varied in size and number and were present largely on the posterior and lateral surfaces of the cord and on the posterior roots.

Fig. 1.—Normal spinal arachnoid, anterior lateral surface, showing trabeculae; the dark masses are cell clusters and corpora arenacea. Ehrlich's hematoxylin and eosin; × 60.

They were less in evidence over the anterior surface of the spinal cord (fig. 1). Many of these clusters or nests contained calcified bodies—corpora arenacea—within their centers. These bodies were often surrounded by dense collections of nuclei with rather scant or no visible cytoplasm. In some instances the cells or nuclei were elongated and compressed and formed concentric layers which surrounded the calcified bodies. The cytoplasm of the cell nests was more visible at the margins of the nests, but they were vacuolated, often merged with the cytoplasm

of the adjacent cell bodies and, as mentioned, suggested a syncytial structure (fig. 3). Simple hypertrophy of the cells or their nuclei, some appearing as giant cells, was a common observation. In many instances the cells appeared degenerated. They were poorly stained, swollen and vacuolated, with a ringlike (ballooned) appearance of the nuclei and an absence of chromatin granules.

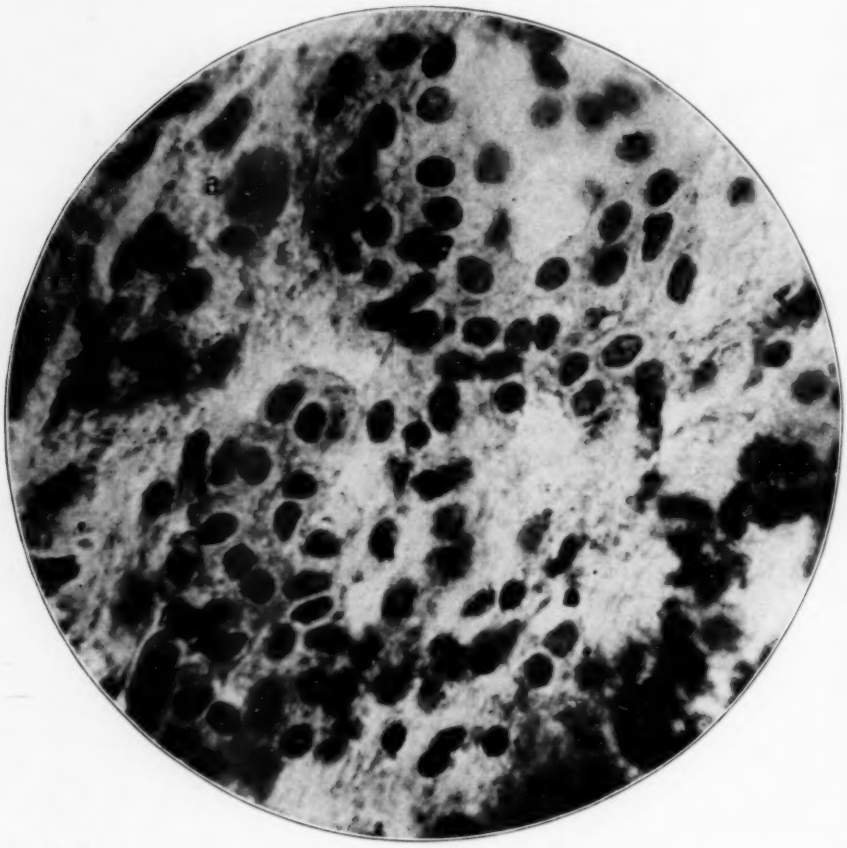

Fig. 2.—Tabetic type of dementia paralytica, posterior roots, showing mesothelial cells of the spinal arachnoid in active proliferation; (*a*) mitotic figure. Ehrlich's hematoxylin and eosin; × oil-immersion.

CHANGES IN THE ARACHNOID CELLS AS OBSERVED IN INDIVIDUAL CASES

Only a few instances will be described here to show the differences in the cell reaction.

Tabes Dorsalis.—Hyperplasia of the cells was especially marked. The cells were found largely in numerous dense nests, forming veritable

whorls (fig. 4). In no other condition were the nests so numerous. Scattered throughout the arachnoid were also a great number of the smaller cells. These showed as small nuclei, deeply stained, and were evidently the younger arachnoid cells. They appeared rounded and somewhat elongated. Some of the cells were hypertrophied and consisted of irregular cell bodies, at times vacuolated and containing from

Fig. 3.—Arachnoidal cells in multiple sclerosis. They show marked swelling, vacuolation or spongy appearances of the cytoplasm with a tendency to coalesce and form a syncytial structure. Hematoxylin and eosin; × oil-immersion.

two to three nuclei. In other instances, the nuclei of the larger type were greatly swollen and appeared as rings with dustlike chromatin granules. In the meshes of the trabeculae the cells resembled macrophages and were quite numerous. The numerous other cells observed, such as lymphocytes, polyblasts and plasma cells, which belonged to

the pia and its prolongations, will be merely mentioned here. In addition, mention should be made of the presence of lipoids in the subarachnoid space. Stained with scarlet red, droplets of fat of various sizes were seen in the arachnoid membrane. They were scattered freely; many of them were within the cells, but they were mostly gathered within the cell clusters. In some instances the lipoids appeared as incrustations, as droplets around the nuclei or over the cell bodies.

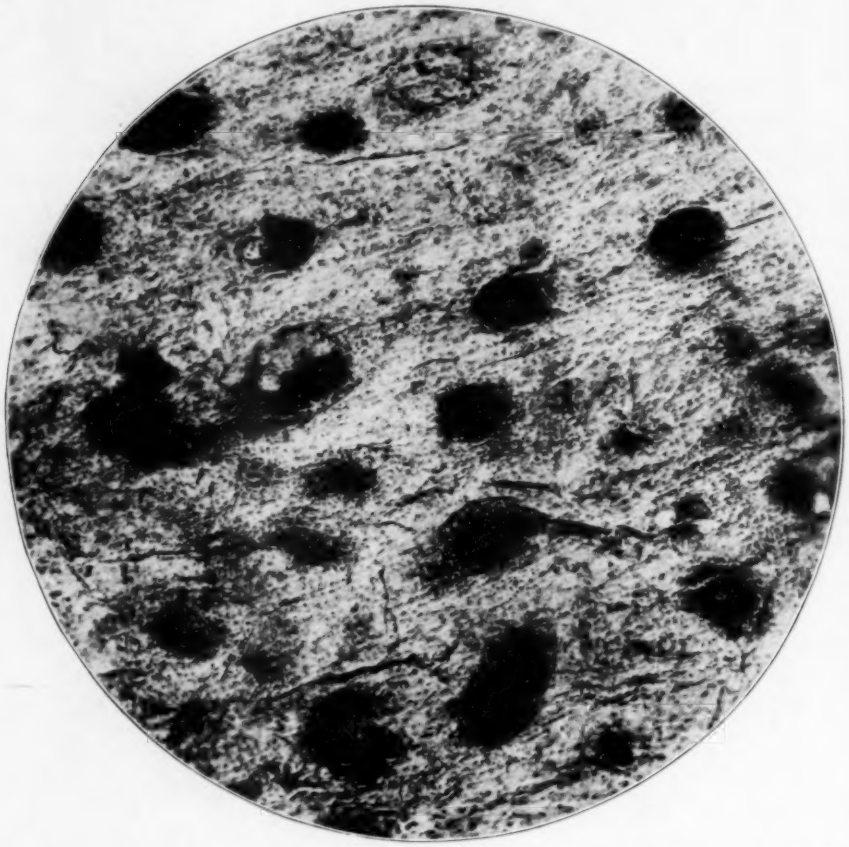

Fig. 4.—Tabes. The numerous dark masses are cell clusters or nodules of mesothelial cells. Some contain calcified bodies. Contrast with figure 5. Hematoxylin and eosin; × 80.

Multiple Sclerosis.—In contrast to tabes, the arachnoid cells in this condition were diffuse. They densely infiltrated the arachnoid throughout; the dense and numerous clusters seen in cases of tabes were here replaced by small clusters of cells, which formed loose collections of nuclei. Typical cell nests with and without calcified bodies, though

present, were few (figs. 5 and 6). Variations in the size of the nuclei of the arachnoid cells were marked. Many of them were huge, while some appeared like empty rings, undergoing degenerative changes. There were also a considerable number of erythrocytes and occasional lymphocytes scattered through the arachnoidal tissue. The latter were considerably fewer than those found in tabes. Fat droplets were also numerous. They were scattered throughout the arachnoid membrane and, as in tabes, were collected largely in the cell clusters.

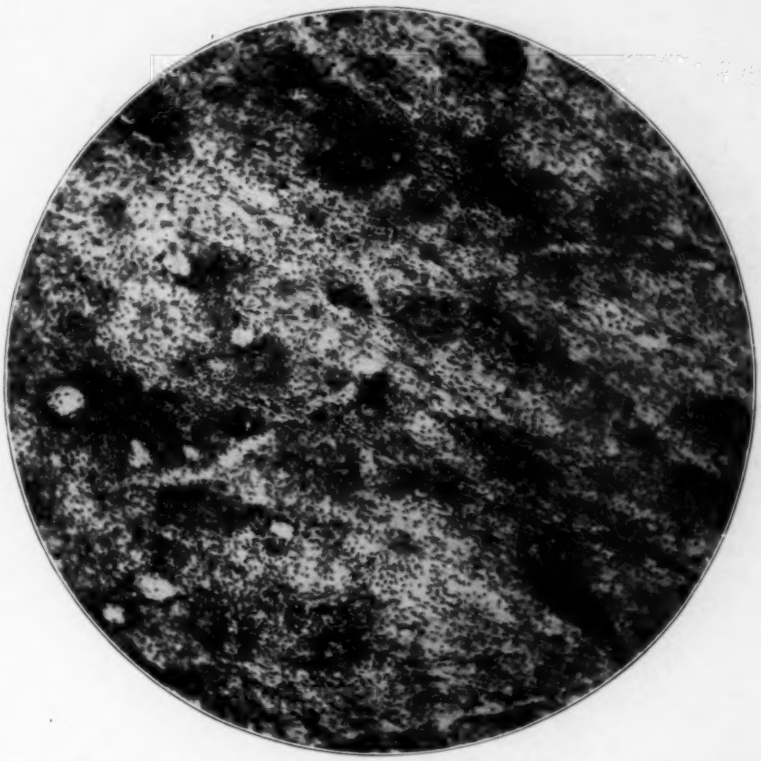

Fig. 5.—Multiple sclerosis. Localized and diffused infiltrations of mesothelial cells of the spinal arachnoid; the dark bodies are corpora arenacea. Hematoxylin and eosin; × 80.

Multiple Myeloma; Neurinoma.—Cell changes similar to those in multiple sclerosis were present in these conditions, except that the cell clusters and nests were more numerous (fig. 7). The cells lining the trabeculae, however, were actively proliferating. Mitotic figures were often seen. A great number of the cells resembled fibroblasts and macrophages. Many of the cells were irregular in shape and of large size, in cases of neurinoma, resembling giant cells. They usually contained from two to three irregularly shaped nuclei and occasionally had

deposits of calcium within their cytoplasm. Scattered between these cells were often erythrocytes, blood pigment granules and a few polymorphonuclear leukocytes. The pavement-like character of the cells with their intercellular lines was clearly defined. In others, however, the cytoplasm showed vacuolation; the nuclei were pale and swollen, exhibiting degenerative changes.

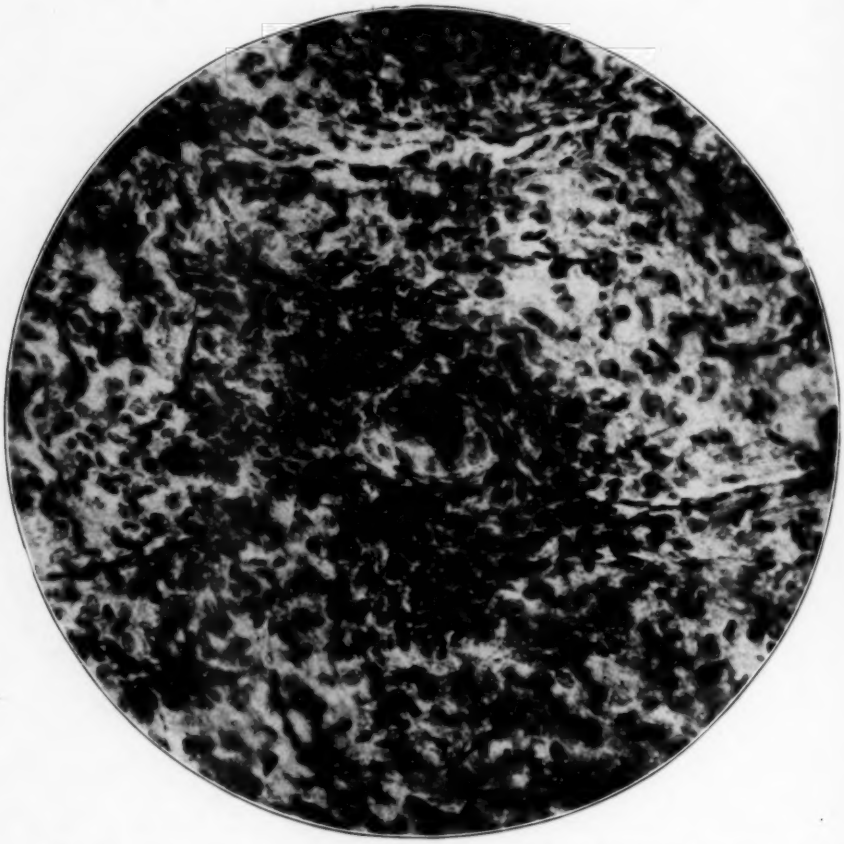

Fig. 6.—Same section as figure 5, under higher magnification, showing a cell cluster or a cell nest with beginning calcification of the cells in the center. Hematoxylin and eosin; × 320.

Subacute Combined Degeneration of the Spinal Cord.—The arachnoid cells, as well as the cell clusters or nests, were moderately increased in number. Corpora arenacea were numerous, many being of irregular shape. There were many young arachnoid cells with a deeply stained nuclear membrane. Mitotic figures were encountered at times. The intercellular markings were clearly discernible, and their cytoplasm was

deeply stained. Many of the cells resembled fibroblasts with long cytoplasmic processes. Degenerating cells appeared more frequently. These were either vacuolated or contained calcium salts; some were broken down and showed as naked nuclei. The latter were often greatly increased in size; their chromatin granules were sparse and dustlike or absent and replaced by deposits of calcium. In this condition, as well as in

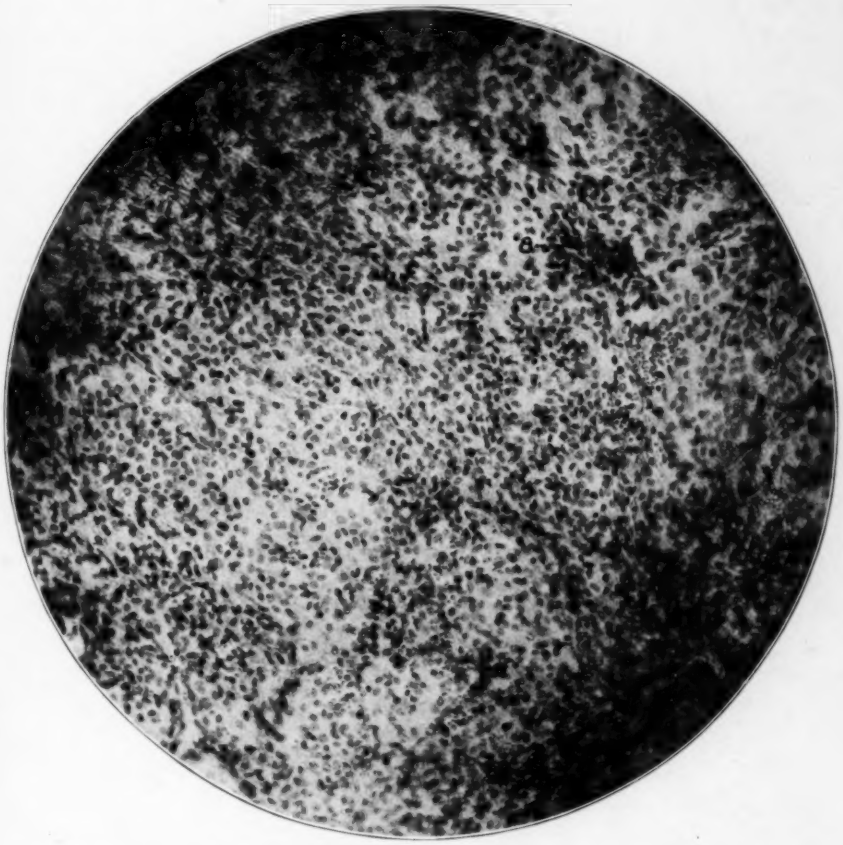

Fig. 7.—Multiple myeloma. Diffuse infiltration of the mesothelial cells throughout the spinal arachnoid. (*a*) Tendency to cluster formation. Hematoxylin and eosin; × 120.

myeloma, fat droplets were found in moderate amounts. They were scattered more or less throughout the membrane.

Myelomalacia.—Few cell clusters or nests were found; instead there was a moderate generalized increase in the number of arachnoid cells. Marked reaction of the latter, however, was noted in the region of the softened portions of the cord, especially on the posterior and lateral sur-

faces. Mitotic figures were frequently present. There were many macrophages, apparently of arachnoidal origin, while some were phagocytes with cell inclusions. Many resembled fibroblasts. The latter, derived from the trabeculae, were large and hypertrophied. Interspersed among the various proliferated cells were many polymorphonuclear leukocytes, erythrocytes, polyblasts, lymphocytes and young fibroblasts. These were secondary to the degenerative changes present in the pia-arachnoid. Degenerative changes in the arachnoid cells were also noted, and were similar to those described in the previous cases. The lipoids in this condition were found in especially large quantities. In some areas the microscopic field was densely covered by reddish droplets and incrustations.

Tabetic Dementia Paralytica; Syphilitic Meningitis; Spinal Syphilis.—In tabetic dementia paralytica there was marked active proliferation of the arachnoid cells along the posterior roots as shown by numerous mitotic figures. In other areas (posterior surface) there were also many macrophages intermingled with fibroblasts, polyblasts, plasma cells and lymphocytes. These cells were especially numerous in spinal syphilis and syphilitic meningitis. In the latter condition, the fibroblasts were the most numerous. They were difficult to distinguish from the hypertrophied and proliferated detached arachnoid cells lining the trabeculae. Other areas, in addition, contained erythrocytes, a number of polymorphonuclear leukocytes and phagocytes. Cell clusters were found more or less increased in number, with many calcified bodies. Degenerative changes of the cells were similar to those in other cases. In tabetic dementia paralytica, moderate amounts of lipoids were present. They appeared as minute droplets scattered within the meshes of the membrane as well as within the cells. In spinal syphilis, the fat droplets were considerably more numerous and larger and were scattered throughout the arachnoid membrane as well as within the cells.

The remaining cases need not be described as they all showed practically similar changes. In senility there was a moderate increase in the arachnoid cells with a considerable increase in the number of calcified bodies.

COMMENT AND SUMMARY

The changes in the arachnoid cells outlined in this comparative study of thirty-five cases were mild in some instances; in others, they were marked, but they were present in practically every case. The changes were: (*a*) simple swelling of the cells, (*b*) an active proliferation, (*c*) the formation of macrophages, (*d*) a focal hyperplasia with formation of cell clusters, (*e*) a diffuse infiltration with a tendency to syncytial formation and (*f*) frequent regressive changes, such as calcification.

A slow hyperplasia of the arachnoid mesothelium in the form of localized cell clusters or nests, often associated with the presence of corpora arenacea, was first described by Meyer,[4] in 1859. He considered them a product of a "chronic irritation." Since then, others have reported similar cell clusters in the arachnoid of the brain and spinal cord in man and animals, and have ascribed as the cause the influence of advanced age (Schmidt,[5] Cushing and Weed [6] and Essick [7]). The cell clusters were found within the arachnoid membrane and on the outer surface, sometimes in the form of psammoma bodies (Cushing and Weed [6]) and occasionally as dural endotheliomas (Schmidt,[5] Weed [8] and Brockbank [9]). Trauma and infection were found to be important etiologic factors in the fifty cases studied by Winkelman and Wilson.[10] They constantly found a tendency to localized proliferation of the arachnoid cells in the cerebral and arachnoid of persons past middle life. On the other hand, Odyniec [11] described cell clusters in the spinal arachnoid (twenty cases), but did not regard age or inflammation as an influencing factor. Weed,[8] Essick [7] and Ayer,[12] however, have shown experimentally that the cells lining the subarachnoid cavity respond to various stimuli (carbon granules, laked blood and infection). These changes consisted in an increased size of the cells, their active proliferation, phagocytic activity and the formation of macrophages. Undoubtedly, any other substance harbored within the spinal fluid must act in a like manner on the arachnoid cells (Hassin [13]). The reaction

4. Meyer, L.: Die Epithelsgranulationen der Arachnoidea, Virchows Arch. f. path. Anat. **17**:209, 1859.

5. Schmidt, Martin B.: Ueber die Pacchionischen Granulationen in ihr Verhältniss zu den Sarcomen und Psammomen der Dura Mater, Virchows Arch. f. path. Anat. **170**:429, 1902.

6. Cushing, Harvey, and Weed, Louis H.: Studies on the Cerebrospinal Fluid and Its Pathology, Bull. Johns Hopkins Hosp. **26**:367, 1915.

7. Essick, C. R.: Formation of Macrophages by the Cells Lining the Subarachnoid Cavity in Response to the Stimulus of Particulate Matter, Washington, Carnegie Inst. Contrib. Embryol., 1920, no. 272, p. 379.

8. Weed, Louis H.: An Anatomical Consideration of the Cerebrospinal fluid, Anat. Rec. **12**:461, 1917.

9. Brockbank, T. W.: Proliferation of the Arachnoid Cell in and Arourd the Dura Mater, Arch. Neurol. & Psychiat. **22**:444 (Sept.) 1929.

10. Winkelman, N. W., and Wilson George: Localized Proliferations of the Arachnoid, Arch. Neurol. & Psychiat. **14**:46 (July) 1925.

11. Odyniec: Die Endothelknoten in der Arachnoidea spinalis und ihre pathologische Bedeutung und die Genese der Sandkörperchen, Inaug. Diss., Zurich, 1908.

12. Ayer, J. B.: A Pathological Study of Experimental Meningitis from Subarachnoid Inoculation, Monograph of the Rockefeller Institute, 1920, no. 12, p. 26.

13. Hassin, G. B.: Tabes Dorsalis, Arch. Neurol. & Psychiat. **21**:311 (Feb.) 1929.

must necessarily vary in intensity, depending on the nature of the disease process.

By comparing the photomicrographs presented here to illustrate a few of the conditions found in the arachnoid, one can see that arachnoid cells do vary in number, shape, arrangement in foci, etc. It is probable that these changes in the mesothelium are caused by physicochemical changes in the cerebrospinal fluid. The state of the parenchymatous brain tissue, moreover, is reflected in the cerebrospinal fluid, for the perivascular spaces of the brain empty into the subarachnoid space.

The fact that lipoid products of degeneration are often found in the arachnoid cells is evidence in favor of the view that the perivascular spaces discharge products of degeneration into the subarachnoid space. This can be shown by staining the arachnoid with scarlet red.

In cases of myelomalacia, the amount of lipoids found was greater than in any other condition. The visual field in some areas was densely covered with numerous droplets of lipoids of various sizes. Some were irregular in shape. They enveloped the nuclei, adhering to their edges, or covered the surface as if they formed incrustations. In some conditions, such as tabes, large accumulations of lipoids were present in the cell clusters. They filled up the spaces between the cells. It was, however, not possible to tell whether the cells themselves harbored the lipoids as the foci were so dense. In subacute combined degeneration of the cord, multiple sclerosis, tabetic type of dementia paralytica, spinal syphilis and myeloma, the lipoids were also abundant. Many of the cells were completely filled with minute droplets. In these conditions also the lipoids were sometimes present as irregularly shaped incrustations. In contrast, normal cords contained much smaller amounts of lipoids in the arachnoid.

CONCLUSIONS

1. Changes in the arachnoid cells are of rather common occurrence in diseases of the central nervous system.

2. They are mainly progressive, the most striking being the formation of clusters.

3. The cell changes vary in intensity and extent according to the type of the disease.

4. The changes in the arachnoid may depend on the physicochemical properties of the cerebrospinal fluid.

News and Comment

INTERNATIONAL NEUROLOGICAL CONGRESS

The International Congress will be held at Berne, Switzerland, from Aug. 31 to Sept. 4, 1931. The following preliminary programs have been arranged for the various subjects which will be presented during the morning sessions and one afternoon session of the Congress:

A. Diagnostic and Therapeutic Procedures (Surgical and Otherwise) in Tumors of the Brain.—The program is arranged by Prof. Max Nonne, Hamburg, and will be presented during the morning and afternoon sessions on Monday, August 31.

1. Diagnosis

(*a*) Clinical Symptomatology

Reporter: Sir James Purves-Stewart, London

Coreporters: Clovis Vincent, Paris
Giuseppe Ayala, Rome
Foster Kennedy, New York (Tumors of the Temporosphenoidal Lobes: Subfrontal Syndromes)

(*b*) Histologic Diagnosis

Reporter: Percival Bailey, Chicago

Coreporters: Wilder Penfield, Montreal
Bertold Pfeifer, Nietleben, Germany (Callosal Puncture)

(*c*) Roentgenologic Diagnosis

Reporter: Arthur Schüller, Vienna

Coreporters: Ernest Sachs, St. Louis (Roentgenology in Neurosurgery)
H. W. Stenvers, Utrecht

(*d*) Ventriculography and Encephalography

Reporters: Walter Dandy, Baltimore (Tumors of the Hemispheres and of the Posterior Cranial Fossa)
Otto Foerster, Breslau (Brain Tumors; Pseudotumors)

Coreporters: Francis Grant, Philadelphia
Egas Moniz, Lisbon (Arterial Iodide Injection)

(*e*) Serodiagnosis

Reporter: Victor Kafka, Hamburg

Coreporters: Frank Fremont-Smith, Boston
H. Bohnenkamp, Würzburg, Germany (Electrical Resistance)

2. Therapy

(*a*) Surgical Therapy

Reporter: HARVEY CUSHING, Boston

Coreporters: THIERRY DE MARTEL, Paris
OTTO FOERSTER, Breslau
H. OLIVECRONA, Stockholm
CHARLES H. FRAZIER, Philadelphia
LUDWIG PUUSEPP, Tartu, Esthonia

(*b*) Roentgenologic Therapy

Reporter: A. BECLÈRE, Paris

Coreporters: H. CAIRNS, London (Radium)
M. HIRSCH, Vienna (Radium)

(*c*) Organotherapy

Reporter: TRACY J. PUTNAM, Boston

B. Muscle Tonus, Anatomy, Physiology and Pathology.—The program is arranged by Sir Charles Sherrington and will be presented at the morning session on Tuesday, September 1.

1. Anatomy

Reporters: S. WALTER RANSON, Chicago (The Nuclei and Tracts Concerned in the Postural Responses Elicited by Stimulation of the Mesencephalic Tegmentum)

KEN KURÉ, Tokyo (The Tonus Tracts and Their Terminal Plates in Muscle)

2. Experimental Physiology

Reporters: G. G. J. RADEMAKER, Leyden

GRAHAM BROWN, Cardiff

E. A. SPIEGEL, Vienna (Zur Pharmakologie der zentralen Tonusregulation)

L. ASHER, Berne (Influence of the Sympathetic Nervous System on the Skeletal Muscles)

DENNY BROWN, London (The Part Played by Afferent Muscular Nerve-Endings in Postural [Tonic] Reflexes)

V. VON WEIZSÄCKER, Heidelberg (Electrical Analysis of Tonus)

3. Pathology

Reporters: F. BREMER, Brussels (Pharmacologie du tonus normal et pathologique)

LEWIS J. POLLOCK and LOYAL DAVIS, Chicago (The Relation of Modifications of Muscle Tonus to the Interruption of Certain Anatomic Pathways)

4. Clinical

Reporters: S. A. KINNIER WILSON, London (Disorders of Tonus at Different Physiologic Levels, with Special Reference to the Cortex)

R. CRUCHET, Bordeaux (Relation of Tonus to the Parkinsonian Syndromes)

J. RAMSAY HUNT, New York (The Static and Kinetic Systems and Their Relation to Muscle Tone)

F. NEGRO, Turin (Alterations of Muscle Tonus in Extrapyramidal Syndromes)

A. THÉVENARD, Paris (Le phénomène de la poussée)

SIR CHARLES SHERRINGTON

C. Acute Nonsuppurative Infections of the Nervous System.—The program is arranged by Prof. Georges Guillain, Paris, and will be presented at the morning session on Thursday, September 3.

Reporters: OTTO MARBURG, Vienna (Introduction to the General Pathology of Acute Infections of the Nervous System)

GEORGES MARINESCO, Bucarest (Pathogénie de certaines encéphalomyélites à ultra-virus)

J. G. GREENFIELD, London (The General Pathologic Anatomy of Acute Infections of the Nervous System)

AUGUST WIMMER, Copenhagen (General Clinical Studies of Acute Infections of the Central Nervous System)

H. PETTE, German (Rabies; Borna's Disease; Landry's Paralysis)

ANDRÉ THOMAS, Paris (Zona; the Herpetic Infections)

L. VAN BOGAERT, Antwerp (Vaccinal Encephalitis, Varicellar Encephalitis; Nonclassified Cases)

V. M. BUSCAINO, Catania (Psychiatric and Biologic Questions in Connection with Acute Infections of the Nervous System)

PROF. GEORGES GUILLAIN

D. The Rôle of Trauma in the Production of Nervous Symptoms.—The program is arranged by Prof. O. Rossi, Pavia, and will be presented at the morning session on Friday, September 4.

Reporters: PROFESSOR ROSSI, Pavia (Importance and Limitations of the Subject; General Discussion)

CHARLES P. SYMONDS, London (Commotio Cerebri; Diagnosis and Treatment of the Cerebral States Following Head Injuries [Exclusive of the Ordinary Brain Injuries])

JEAN LHERMITTE, Paris (Spinal Cord Injuries [Commotio medullae spinalis])

ARTHUR VON SARBÓ, Budapest (Injuries of the Peripheral Nerves; Microscopic Traumatic Changes in the Nervous system)

O. VERAGUTH, Zürich (Rôle of Trauma in Producing Some Nervous Diseases [Cerebral Tumor, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, etc.])

P. Rio del Hortega, Spain (Traumatic Changes in the Glia as Explanatory of Some Disorders of Nervous Function)

F. Naville, Switzerland (Effects of Some Special Traumas [Electrocution, etc.])

Smith Ely Jelliffe, New York (The Psychologic Level in Trauma of the Nervous System)

The arrangement of the programs for the afternoon sessions will probably be completed during the early part of 1931, and definite announcement will be made as soon as possible. The present plans of the Program Executive Committee are to hold sessions of the entire Congress on each afternoon. If, however, the number of papers deserving to be presented is large, it may be desirable to divide the topics under various headings and to hold separate sessions of the Congress on the various afternoons. The members of the Congress may then attend any session in which they have special interest.

Special clinics will be given for the members of the American delegation who are expecting to make the tours, which have been arranged by Thos. Cook & Son. In all probability, these clinics will be held at Paris under the direction of Professor Guillain or one of his associates, at Amsterdam under the direction of Professor Brouwer or one of his associates, at Zurich by Professors Maier and Minkowski, and at Pavia by Professor Rossi or one of his associates.

To enable the Secretary-General to complete the authoritative list of members, all applications for membership should be in his hands by April 15.

Bernard Sachs, *President.*

Henry Alsop Riley, *Secretary-General.*

AMERICAN NEUROLOGICAL ASSOCIATION

The Fifty-Seventh Annual Meeting of the American Neurological Association will be held in Boston, on May 27, 28 and 29, 1931.

Obituary

CONSTANTIN VON MONAKOW

1853-1930

One of the most picturesque figures in the neurologic world has passed away in Constantin von Monakow. He was a giant in stature, a man of unusual force and dignity, the creator of his own renowned institute, the biologizer of man, neurologist, but neurobiologist rather than neurophysiologist, and neurohormonist.

The writer attended von Monakow's first or second course on anatomy of the brain, perchance the same course that H. H. Donaldson attended in 1886. Von Monakow had spent nine years as assistant in St. Pirminsberg, a small state hospital above Ragez. With a taste of von Gudden's work, he accepted the appointment as he came back from a trip to South America as ship surgeon. Experimental anatomy of the brain dealing with the optic apparatus, and a wide range of experimentation that brought him into contact with Munk, gave von Monakow a name of distinction before he came to Zürich as privatdozent. To the neurologic laboratories of Huguenin, Forel and Honegger, von Monakow added another one of those very personal centers of work, devoted extensively to the study of secondary degeneration of human cerebral lesions, with particular attention to the cortex-dependent parts, and in vigorous competition with Flechsig's myelinization methods and Hösel's claims. The study of the thalamus, then the study of the red nucleus and the development of the publication of the "Arbeiten" of his laboratory laid the foundations for the *Schweizer Archiv für Neurologie und Psychiatrie*. In the meantime, the large volume in Nothnagel's handbook led to a development of functional interests; the building up of the evolution of the motor functions, the conservative studies on aphasia and apraxia, also on a functional rather than a strictly anatomic ground, and the diaschisis concept, are the outstanding products of the first two decades of the new century. After the war, von Monakow had the overwhelming urge for a broad comprehension of human life in the light of his growing clinical interest in the neuroses and life-problems, which culminated in a collaboration with Mourgue and a biologic-philosophic retrospect of, rather than an introduction to, the study of neurology and psychopathology. Untiring, he worked as ever after his institute was taken over by Minkowski, and like a soldier he died with his goose-quill pen in hand, struck in the midst of a sentence. A fighter and yet a friend, stubborn in his accepted views and yet open to wide

perspectives, in the end he allowed himself full sway to give us his testament of a rich and forceful career, a life of rare devotion to a monumental conception of living science.

Among the productions of his last years we may hope to see published an autobiography and a wealth of ponderings of a Tolstoyan urge which made contact with the vigorous personality during the last years a great privilege and delight.

He will be missed at the International Congress of Neurology of 1931. He had been a strong member of the International Brain Commission, and, while perhaps rather too personal a personality to be a sweeping and popular leader, he was a towering figure in all the gatherings he joined. The University of Zürich rose to a great duty and privilege when it decided to keep together the unique collection, and the workshop and the opportunity for further development of the Monakow Institute under his pupil and successor Minkowski.

Adolph Meyer, M.D., Baltimore.

Abstracts from Current Literature

LARYNGEAL PARALYSES: A NEUROLARYNGOLOGIC STUDY. TERRACOEL, EUZIÈRE and PAGÈS, Rev. d'oto-neuro-opht. **8**:241 (April) 1930.

This report by two neurologists and a laryngologist to the Fourth Congress of Oto-Neuro-Ophthalmologic Societies, at Brussels in June, 1930, consists of five parts: anatomicophysiologic considerations, the symptomatic elements of laryngeal motor paralyses, the principal clinical types of laryngeal paralyses, associated laryngeal paralyses and the practical interest of laryngeal paralyses.

In the first part, the general physiology is first discussed. The larynx has, in addition to those of respiration and voice, a third function: protection of the inferior respiratory tract. The articulations and musculature are described, and the fact is emphasized that the dominant action of the muscles as a whole is a constrictor one. The larynx is essentially a sphincter. The extrinsic muscles play an important rôle by their synergistic action, not only in phonation, but in the protection of the lower air tract by the fixation, elevation and lowering of the laryngeal framework. After describing the researches and experiments of numerous writers in locating the cortical, cerebellar and bulbar centers and pathways, the following facts seem to be established: 1. A cortical center exists for the laryngeal functions, probably located at the level of the inferior part of the ascending frontal convolution in the fold between it and the third frontal gyrus. 2. The antagonistic motor centers, abductor and adductor, are so closely associated in the cortex that it is necessary to resort to the arts of experimentation to dissociate their functions. 3. The influence of each cortical motor center appears to be exercised on both halves of the larynx, but with a marked predominance on the opposite side. 4. The motor representation in the bulb, for each of the functions of the larynx, has centers distant one from the other.

The bulbar centers preside over the reflex acts (automatic respiration and reflex cries) and exercise a trophic action on the muscles. The cortical centers are in relation with voluntary acts (talking, singing, forced respiration). These data are in harmony with the most recent ideas of general neurobiology, notably the work concerning the integration of motor functions in their relation to the cyto-architectonic development of the nerve centers. The peripheral motor pathway is represented by the superior and inferior laryngeal nerves. The former arises at the level of the internal part of the plexiform ganglion; rarely, it arises by two roots from the pneumogastric or from both the vagus and the glossopharyngeal nerves. It divides into two branches. The external branch supplies the cricothyroid muscle with motor fibers and the mucosa of the subglottic region with sensory fibers. The internal branch supplies sensory fibers to both surfaces of the epiglottis and to the upper part of the larynx, including the under surface of the vocal cords and the mucosa on the posterior face of the cricoid and arytenoid cartilages. There are rich anastomoses with the pharyngeal plexus, the sympathetic (superior cervical ganglion, carotid plexus of Haller) and the opposite internal laryngeal nerve. There exist, also, motor fibers for the hyoid and styloid muscles, the lateral crico-arytenoideus and the arytenoideus. Embryologically, anatomically and functionally, the external laryngeal nerve must be considered a collateral branch, perhaps a distinct nerve.

The inferior laryngeal nerve is described, emphasis being placed on its numerous anastomoses, especially that formed on the posterior face of the cricoid by a pharyngeal branch and the recurrent nerve. There has been a long controversy over the rôle of the laryngeal nerves. The question is: Are the superior and inferior laryngeal nerves exclusively motor and sensory, or are they mixed nerves? The results of experiments made on animals and on human beings are reviewed. The net results of all the experiments on animals are: that it is impossible to

generalize a single observation and that the recurrent nerve in the dog appears to harbor sensory fibers in its peripheral portion, but these fibers appear to be brought to it by the intermediary of the loop of Galen on the posterior surface of the cricoid. In man, it seems demonstrated that there are numerous anastomoses between the internal branch of the superior laryngeal and the motor fibers from the recurrent laryngeal to the arytenoideus muscle, although Collet's experiments go to show that there is no intermingling of the nerves of the two sides across the median line. The conclusion is that in animals the superior laryngeal nerve is essentially sensory and accessorily motor. The recurrent is essentially motor and sensory only by the supply of sensory fibers from the superior laryngeal through the loop of Galen. In man the superior laryngeal nerve is essentially sensory, but it is also motor. The recurrent is essentially motor. Its sensory rôle can only be suspected from comparison with that of animals, the existence of anastomoses between the two laryngeal nerves, the fact that it sends branches to glandular elements and the tracheal mucosa, and the fact that general researches seem to demonstrate the mixed character of all nerve elements.

The researches of E. Hédon have established the presence of vasodilator and secretory fibers for the laryngeal mucosa in the superior laryngeal nerve of the dog. Stimulation of the sympathetic nerves at the level of the loop of Vieussens produced a vasoconstriction of the corresponding half of the larynx, but section or stimulation of the recurrent nerve caused no modification. In man, anatomic researches have shown the frequency of anastomosis between the sympathetic and the laryngeal nerves. The superior laryngeal nerve innervates the cricothyroid muscle. The inferior laryngeal nerve innervates all of the other muscles. The innervation of the arytenoideus appears to be bilateral.

In part 2 of the paper, the symptoms of motor paralysis are considered. The larynx is peculiar in that a single nerve supplies motor impulses to antagonistic muscles; the openers and the closers of the glottis. Semon and Rosenbach, in numerous publications, affirmed "the biologic inferiority of the crico-arytenoideus posticus, the sole dilator of the glottis" (Semon's law) and called attention to the tendency of the dilator fibers to be affected either exclusively or before the constrictor fibers. Thus, the median position occupied by the vocal cord is due to an incomplete paralysis of the recurrent nerve. This paralysis eventually may progress no further or it may be completed by paralysis of the constrictors, in which latter event the cord occupies the so-called cadaveric position. Numerous reports of researches on this question followed, the most notable of which were those of Lermoyez, Griner, Brockaert and Dufourmentel. Various opinions were offered in explanation of this inferiority of the dilators, some on anatomic grounds: the peripheral situation of the dilator fibers, their numerical and dynamic inferiority and their unfavorable insertion; some on biologic grounds: rapid postmortem loss of electric excitability of the dilator muscles and nerve fibers; less resistance to external noxious influences.

As to the law of Semon-Rosenbach, it is necessary to refer to two facts: In certain cases it is difficult to ascertain with exactitude the position of the cord, and the term "cadaveric position" is inexact. Brockaert's term, "intermediate position" is more descriptive of the cord in the living person. Several facts tend to invalidate this law. Ruault cut the recurrent nerve in a laryngeal hemiplegic with the cord in the median line; no change occurred in its position. Mygind and others found the same degree of atrophy in the constrictors as in the dilators in cases of median paralysis. Lermoyez and Lombard never observed the passage of the cord from the median to the intermediary position, and in those cases of intermediary paralysis which end in recovery, there is no return to the median position. Collet, in cases of laryngeal hemiplegias from war wounds, after long observation found the position of the cords unchanged. It is certain that complete section of the recurrent nerve in surgical operations results, in a great majority of cases, in the cord lying in the intermediary position.

It appears that Semon's hypothesis is not sufficient to explain these differences of position. Grabower had a patient with double posticus paralysis with the cords in the median position for several months. On section of the external branch of the

superior laryngeal nerve, the glottis opened. Killian, Wagner, Leichsenring and Hegener obtained identical results either by sectioning or by applying cocaine to the superior laryngeal nerve. In the pathogenic determination, anomalies of innervation must be taken into account; the cricothyroid muscle, the suprahyoid and infrahyoid muscles, the pharyngeal muscles and the association of irritative and paralytic phenomena occupy a place in the foreground. One cannot envisage the same mechanism for a paralysis due to section of the nerve as for one due to compression or to infectious processes. In hemiplegia of the limbs, contractures occur principally in the adductors; the abductors are more affected in flaccid paralysis.

The principal clinical types of laryngeal paralysis are the subject of part 3. Laryngeal hemiplegia is due to a lesion of the recurrent nerve from compression, neuritis or traumatism. In paralysis from aortic aneurysm, the factor of compression seems overestimated. From the beginning, sudden loss of voice is predominant. Immobility of the vocal cord in phonation and in respiration is an essential characteristic of laryngeal hemiplegia. The position of the cord is variable, but most often it is intermediary (cadaveric position). "Every immobilization of the cord of a hemi-larynx, microscopically normal, whatever its position, is a recurrent paralysis." Two phenomena follow: muscular atrophy and deformity, and compensation. Compensation occurs by contraction of the arytenoideus muscle, the cord being forced to the opposite side and the two arytenoids overlapping. The voice is reestablished, but its power and timbre are modified.

Both sensory and motor troubles occur when the superior laryngeal, a mixed nerve, is paralyzed. Sensory disturbances are mostly a disappearance of the reflex sensibility. The general sensibility is blunted but not completely abolished, owing to the multiplicity of the anastomoses. The tension of the cords is affected, the voice is monotonous and rough, the production of sharp sounds is defective and the larynx is rapidly fatigued. The cord is flaccid and undulating, and the mucosa is folded.

Bilateral paralyses of the recurrent laryngeal nerve may arise from the same provocative causes that bring on hemiplegia of the larynx. Certain radicular, nuclear or supranuclear lesions play an important rôle in bilateral laryngoplegias and cause a particular type of paralysis called paralysis of the dilators. In 1868, Ziemssen, on the basis of two cases of bilateral recurrent paralysis, established the essential functional triad on which the diagnosis rests: (*a*) the great waste of air which the efforts of phonation necessitate; (*b*) the complete aphonia which bilateral paralysis engenders, and (*c*) the total paralysis of the recurrent nerve which is not accompanied of itself by dyspnea. The vocal cords lie in the intermediate position and do not move on respiration or on phonation. Advanced cancer of the esophagus, thyroid hypertrophy and aneurysm are the most frequent causes. Evolution of the paralysis of the bilateral recurrent nerve is by two phases: (1) bitonal voice, one cord being in the intermediate position and the other mobile; (3) aphonia, the cords being immobile in the intermediate position.

In 1863, Gerhardt described three cardinal symptoms of the so-called paralysis of the dilators: (*a*) inspiratory dyspnea, principally during sleep; (*b*) intermittent attacks of suffocation, and (*c*) intact voice. The laryngoscopic image is: a paramedian position of the cords; no movement on respiration, and on phonation the movement of one cord toward the other. He did not envisage a lesion of the nerve, but a failure of the posterior crico-arytenoid muscles. Riegel confirmed Gerhardt's observation in 1875, but attributed the condition to a paralysis of the nerves and called it respiratory paralysis. Rosenbach and Semon published their theory in 1880. This respiratory paralysis is seen most often in tabes, typhoid fever, diphtheria, syringobulbia, malaria, lead poisoning, aortic lesions and esophageal cancer. The predominating cause is syphilis.

The pathogenic interpretation of the facts cited is still under discussion. In 1914, Dufourmentel, on the basis of experimental and clinical studies, affirmed the incorrectness of the law of Semon-Rosenbach. He maintained that "every recurrent paralysis must be considered complete as soon as it entails the immobilization of the corresponding vocal cord," and "every cord immobilized by a recurrent

paralysis occupies a paramedian position and departs from this position only as a result of its progressive atrophy," that the division of the paralyses into complete and incomplete should be abandoned and, finally, that the recurrent paralysis caused by tabes differs in no way from bilateral paralyses caused by other diseases.

In 1922, Lermoyez and Ramadier affirmed the value of Gerhardt's syndrome, created "the laryngeal syndrome of Babinski," and retained the hypothesis of "a partial poliencephalitis of the nucleus ambiguus." In 1924, Dufourmentel reaffirmed his views and stated that almost, if not quite all, cases labeled "paralysis of the dilators" are forms of total paralysis of the recurrent nerve; that the visible movement on phonation results from contraction of the cricothyroid and of the laryngeal fibers of the pharyngeal muscles.

In 1927, Truffert reported his researches on animals. After section of the recurrent nerve, the cord was immobilized in one or another position: after section of the posterior branch (dilator) in a median position; after section of the external branch (constrictor) in forced abduction. In the cat there is no bulbar nucleus controlling the function of dilatation of the glottis. Truffert's conclusions were: The diagnosis of paralysis of the dilators must be limited to cases in which suppression of abduction of the cords is accompanied by integral conservation of adduction; total immobilization of a cord, whatever its position, is a recurrent paralysis; it seems that, from a pathogenic point of view, the hypothesis of a bulbar lesion must be abandoned.

Ramadier combated these views and expressed the belief that the confusion between the two forms of laryngoplegia is due to a misinterpretation of the clinical and experimental facts.

Does there not exist between these diametrically opposed opinions a ground of agreement? Recent facts, derived from experiments on man, confirm the opinion of Dufourmentel as to the abolition of the Semon-Rosenbach law. His denial, however, goes too far. It is certain that Gehardt's syndrome exists, as Lermoyez, Ramadier and others maintain. Many reports of paralysis of the dilators differ in their description. One fact is important, that the cord has lost its abduction in the respiratory act and conserves its adduction and tension in phonation. It is understood that the larynx should not show any anatomic lesion.

As to the two forms of paralysis, aphonic and dyspneic, several explanations have been offered: If the paralysis has evolved rapidly the cords are fixed in the median or paramedian position; if more slowly, the cord first affected has time to get into the lateral position while the other is still unaffected. The dyspneic type is due to combined lesions of paralysis and contracture, and the aphonic type to paralytic lesions. The two nerves may not be affected simultaneously, and one may easily conceive that one cord might be paralyzed and the other contracted. Again, syphilis is selective in its action and may pick out only the conductors of abduction, the result being paralysis of the dilators—"respiratory paralysis."

Associated laryngeal paralysis, involving the soft palate, tongue, muscles of the neck and the larynx, was described by Jackson in 1864. Avellis, Schmidt and Tapia contributed observations on associated paralysis, and World War reports added still more. Garcin studied a case with a unilateral syndrome of all the cranial nerves. The syndromes of Wallenberg and of Cestan-Chenais, due to bulbar damage, are mentioned. The latter shows on the side of the lesion a velopalatolaryngeal paralysis, cerebellar disturbances and an oculosympathetic syndrome of Claude Bernard-Horner, and on the opposite side a sensitivomotor hemiplegia with syringomyelic dissociation. In Wallenberg's syndrome there are added to these, sensory disturbances in the sphere of the trigeminus on both sides. To avoid confusion in nomenclature, Vernet established a classification of associated paralyses "based on the lesions of the nerve trunks themselves and on all the methods of association possible of paralyses of the ninth, tenth and twelfth with the laryngeal nerve, the eleventh." This classification establishes with exactitude the symptomatology of damage to each cranial pair and considers the spinal accessory as the chief nerve of phonation and the pneumogastric as a purely sensory nerve. The great sympathetic nerve may be associated with all these forms. Vernet's classification is given.

From an etiologic standpoint, palatolaryngeal hemiplegia (syndrome of Avellis), glossopalatolaryngeal hemiplegia (syndrome of Jackson) and palatoscapulolaryngeal hemiplegia (syndrome of Schmidt) can be of nuclear or radicular origin. The other paralytic associations are, as a rule, of peripheral origin, but Tapia and de Castro have reported two cases with both central and peripheral lesions. None the less, in the majority of cases the associated paralyses are due to endocranial lesions. In all cases of associated paralysis there is a neurologic complex in which the larynx is only a participating element and not a predominant one.

In part 5, laryngoplegias of cerebral origin are first discussed. The exceptional rarity of paralysis of the larynx in hemiplegia is noted. Graeffner studied 200 cases and, after eliminating laryngeal paralyses of bulbar origin, found only 4 cases of motor trouble, located twice on the side of the hemiplegia and twice on the opposite side. It is hard to postulate in these cases a common origin for the hemiplegia and the laryngoplegia. It is difficult to judge of the perfect integrity of the laryngeal muscles by laryngoscopic examination. A slight motor deficiency or secondary contraction may escape notice. An evident laryngeal paralysis in association with hemiplegia is always suspicious. Monakow's theory of diaschisis, a sort of shock from the local brain lesion resulting in a raising of the threshold of excitation of certain groups of neurons and extending down the spine and to the opposite hemisphere, is at the base of the fundamental distinction between temporary symptoms (domain of diaschisis) and residual symptoms (domain of anatomic degeneration). This theory might explain such a case as Garel's in which paralysis of the cord was noted five days after the stroke. The same considerations would apply to laryngoplegias of pseudobulbar type. The authors believe that a transitory recurrent paralysis can occur in cerebral lesions.

The diagnostic value of laryngoplegias depends on whether they are almost pure or are accompanied by neurologic signs. Nevertheless, the laryngoscope may give valuable information of the seat of the lesion and sometimes useful suggestions for the neurologic diagnosis. Most writers consider that a cortical laryngeal paralysis is characterized by a bilateral affection predominating on the side opposite the lesion, and is not accompanied by sensory troubles, atrophy or qualitative modifications of the electric reactions. It is conceivable that the laryngeal manifestations can be the sole evidence of a cortical lesion. Laryngeal examination in suspected frontal lesions, especially tumors, may have important localizing value. In cerebral hemiplegias from a subcortical lesion, laryngoplegias are without diagnostic value. Even when the corticobulbar neurons on each side are involved, it seems that complete paralysis of one or both cords is exceptional. Yet, in view of the possibility of a cortical laryngeal hemiplegia, the possibility of a lesion involving the pyramidal bundles at the level of the cortex must be considered. A laryngoplegia is never present in a pure extrapyramidal syndrome.

Topographic Diagnosis: Speaking in favor of laryngeal paralysis of peripheral origin are: the strict homolaterality, the frequency of laryngeal anesthesia, muscular atrophy with disturbed electric reactions and the association of troubles connected with lesion of multiple nerves or nuclei. Bulbar lesions have an apoplectiform onset, with pyramidal or cerebellar motor disturbances of the limbs, and have associated with them particular symptoms, such as rotatory nystagmus, tachycardia, glycosuria, etc. A lesion of the trunk will be suggested by an associated paralysis, a slow onset and a development over a long time without other symptoms.

Etiologic Diagnosis: In bulbar diseases syndromes of vascular origin (syphilis especially) are to be thought of: syringobulbia, chronic bulbar paralysis, amyotrophic lateral sclerosis, multiple sclerosis, tumor, Heine-Medin's disease and epidemic encephalitis. In the majority of these lesions, a diagnosis cannot be made from the laryngologic examination alone, but must be associated with a methodical clinical examination of the nervous system. Syphilis plays an eminent rôle in the genesis of paralysis of the dilators. Syringobulbia causes characteristic laryngoplegias: paralysis of isolated or small groups of laryngeal muscles or sometimes an almost complete recurrent paralysis, or there may be recurrent

paralysis on one side and paralysis of isolated muscles on the other with a characteristic dissociation of the sensibility. Tabes may exist for a long time with only a laryngeal paralysis to betray its presence. In glossolabiopharyngeal paralysis the larynx is involved late. Multiple sclerosis may cause laryngeal paralysis, especially of the thyro-arytenoideus and the interarytenoideus, which varies from one examination to another. The myasthenic syndrome of Erb-Goldflam is characterized by paresis of the adductors and tensors and is more marked after vocal fatigue; sometimes the dilators are affected and the trouble is exaggerated by repeated deep inspirations.

Radicular or trunk paralyses are often associated with lesions of other nerves, meningeal and other lesions of the base, aneurysm, tumor of the esophagus and diverse mediastinal lesions. In lesions below the emergence of the recurrent nerve there are no laryngeal signs. In lesions of the trunk of the vagospinal nerve above the emergence of the recurrent and below that of the superior laryngeal nerves, the predominating symptom is complete immobility of the cord and is of no help in differential diagnosis. Respiratory difficulty (pseudo-asthma, cough) and especially cardiac signs (acceleration and instability of the pulse, arrythmia) must be looked for. The oculocardiac reflex is important. "If on the diseased side it is absent or slightly accelerated, it speaks for a lesion of the trunk of the vagus." In lesions between the superior laryngeal emergence and the superior third of the plexiform ganglion there are motor and sensory phenomena: anesthesia of the laryngeal vestibule and lack of the otalgia reflex on pricking the superior laryngeal nerve, cough and pain in the thyroid cartilage and cricothyroid paralysis. In lesions above this point there are: palatolaryngeal hemiplegia and anesthesia of the auricular branch of the vagus, or the sign of the tragus (Escat).

Functional paralysis affects the function of the voice exclusively, and the observations change from one examination to another or even during the same examination, as in multiple sclerosis.

Prognostic Value: Laryngoplegias of bulbar origin appearing in the course of a neurologic disease are of grave import, the most dangerous being paralysis of the abductors, which may suffocate the patient suddenly. In syringomyelia with secondary involvement of the bulb, the prognosis is less grave. In the syndrome of Landry, the appearance of laryngeal paralysis indicates the approaching end, and when multiple sclerosis extends to the bulb, laryngeal paralysis is likewise a warning sign. In a general way, all laryngeal paralyses cause fear of a lesion of important bulbar nuclei. It would be desirable to make systematic laryngeal examinations in all neurologic cases in which bulbar extension of the lesion is feared.

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THE TRACTION OF THE CICATRIX ON AND IN THE BRAIN IN TRAUMATIC EPILEPSY IN ITS SIGNIFICANCE FOR THE OCCURRENCE OF ATTACKS AND FOR THERAPY. O. FOERSTER and W. PENFIELD, Ztschr. f. d. ges. Neurol. u. Psychiat. **125**:475 (June) 1930.

Foerster and Penfield base their studies on traumatic epilepsy on two fundamental observations: 1. In traumas that involve one side of the skull the lateral ventricle of this side appears more or less dilated in the encephalographic picture. This condition is present in traumas with and without lesions of the bone. The dilatation is more pronounced in the former than in the latter, especially when there is a bone defect and the skin is adherent to the dura, and the dura to the brain. The wall of the lateral ventricle on the side of the injury appears drawn out toward the site of injury in such cases. Similar observations have been made on the opposite side. Often it has been noted that the ventricular traction toward the site of the bone defect is not alone limited to the corresponding lateral ventricle, but involves the entire ventricular system. The lateral ventricle on the opposite side appears more or less drawn beyond the midline toward the site of the injury, and the third ventricle in the anteroposterior view shows a more or less oblique position, with the upper pole inclined toward the side of the injury. If the injury occurs more or less in the middle, both lateral ventricles often

appear to be drawn upward. The World War taught that the ventricle on the side of the injury became dilated, even before encephalography was practiced. Internal hydrocephalus could often be demonstrated in these cases. Moreover, it appeared to increase with time, because it was found on repeated puncture that the depth to which one had to insert the needle in order to reach the dilated ventricle decreased with time.

2. It has been observed by Foerster and Penfield that in operations in cases of traumatic epilepsy a pull on the dura in the vicinity of the adhesion between it and the brain produced an epileptic attack. Such attacks have been observed on pulling the skin adherent to the dura in these cases. In the twelve cases reported, epileptic attacks were noted in five by pulls on the dura. In cases of traumatic epilepsy with adhesions between the skin, dura and cerebrum, the question therefore arose whether there might not be a permanent traction on the brain, which, in itself, caused epileptic attacks.

Experimental cerebral wounds have been studied by Penfield and Hortega, Penfield and Penfield and Buckley. Briefly stated, they show that in experiments on animals an injury that involves only the dura and not the arachnoid leads to no adhesions. Only when the pia is injured and the brain tissue exposed does there occur a connective tissue reaction with cicatricial adhesions between the dura, arachnoid and pia, or, in other words, between the dura and the cerebrum. If the wound extends more deeply into the brain, hemorrhages and disturbances of the cerebral tissue result. There follow very quickly in this zone large Abräumzellen; astrocytes swell and multiply within and around the wound, and the formation of new vessels follows in the injured zone and its vicinity. Soon a fibroblastic proliferation follows, within the injured zone and on the cerebral surface.

At first the tissue reaction is local. Then the process of contraction of the scar begins, involving a surrounding zone that was not first involved by the injury. In simple meningeal adhesions, the superficial subpial astrocytes develop thick processes which on the one side are directed toward the position of the adhesions, and on the other side are directed in a diametrically opposite direction. Astrocytic processes, which penetrate into the overlying scar and attach their footplates to the vessels therein, can be demonstrated. The "vaso-astral framework," the supporting system of astrocytes and vessels in the brain, is primarily affected in these cerebral wounds. The hypertrophied processes of the astrocytes follow the line of the wound, as if there were a hypertrophy of the astrocytes in reply to the influence of the mechanical traction. This linear arrangement of the astrocytic fibers is present only in the vicinity of the scar.

Foerster and Penfield report twelve cases in which encephalography showed the ventricular deviation clearly. Of these, nine were cases of gunshot injury, two of birth trauma and one a cranial injury caused by a blow. In all of the cases, with two exceptions, there was a more or less pronounced bone defect. The skin was adherent to the dura, and the dura to the cerebral surface. In seven cases there was thinning of the cerebral mantle due to the dilatation of the ventricle.

Case 1 was that of a gunshot wound of the left parietal region, with penetration of the bony fragments into the brain. Six years later the first epileptic attacks occurred. Encephalography showed a marked pulling of the entire ventricular system toward the site of the bone injury. Operation showed the dura firmly adherent to the skin cicatrix at the site of the injury, and adherence of the dura to the edges of the bony defect. In the midst of the defect the brain bulged forth in a cyst formation, as large as a quarter. The dura and the cicatricial formation in the brain were removed. Four years after this operation, there have been no epileptic attacks. Histologic examination of the cicatrix showed that the connective tissue formation coming from the dura penetrated deep into the brain and was composed of numerous collagen fibers and vessels that anastomosed with the structures in the brain tissue. The glial net in the cerebral scar was composed of fine fibers arranged in parallel bundles. These glia fibers were included in the cell cytoplasm, and were in close relation to the nuclei that lay scattered throughout the tissue. The nuclei appeared like astrocytic nuclei, but

the cytoplasm was not star-shaped. Often the processes and fibers were densely packed, and they sent out long tail-like formations in places. The glial part of the cerebral cicatrix contained no nerve cells, but did contain scattered nerve fibers which were thin and appeared to be fragmented. The number and caliber of these nerve fibers were such, however, that for all practical purposes the cerebral scar could be considered as lacking in nerve fibers. The astrocytes were of the "sprawling type" and inserted their feet on the vessels. These astrocytes were seen especially in the region of the ventricular ependyma. The oligodendroglia appeared normal. When stained, the microglia appeared to be normal.

Case 2 was that of a gunshot injury of the right parietal region, with the onset of epileptic attacks one year later. Encephalography showed marked pulling of the right ventricle to the defect, together with a displacement of the entire ventricular system. Operation showed the same sort of process as in other cases: adherence of the skin to the dura and of the dura to the brain, and the presence of a cerebral cicatrix. Microscopic examination showed numerous vessels between the dura and brain with the penetration of connective tissue into the brain in many places. Glia fibers were less numerous than in case 1. The white substance under the dura showed softening. The astrocytes were markedly injured and deformed. Perivascular gliosis was marked in many places.

Case 3 is of great interest. It concerned a superficial gunshot wound of the left parietal region without a bony defect. Eleven years after the injury, the first epileptic attacks occurred. Encephalography showed only a slight pull of the ventricular system toward the site of the injury. At an operation the dura was found to be adherent to the area of contusion in the brain, and after excision of the dura around this area the brain sank in about 1 cm., demonstrating the pull exerted by the scar and adherent dura. In general the histologic process was similar to that in the other cases.

Case 4 concerned a gunshot injury of the right occipital region with a bone defect. Epileptic attacks began to occur one year after the injury. The skin in the area of the bony defect was firmly adherent to the dura, and the dura to the brain. The posterior ventricular horn was pulled over to the side of the injury. The scar was excised as in the other cases, and showed fibrous tissue penetrating from the dura into the brain, but not very deeply. Adjacent to this zone was a glial zone composed of thin fibers arranged in parallel bands, with astrocytes and some giant cell formation. The connective tissue and glia fibers were arranged in more or less parallel rows.

Case 5 concerned a marked traumatic injury of the left cerebral hemisphere following forceps delivery, with only a right hemiparesis as a result of the extensive cerebral injury. Epileptic attacks began to occur when the patient was 14 years of age, and at 19 two large cysts with a scar lying between them were removed at an operation. The cysts were only dilated ventricular pockets. The scar formation lying between these consisted of bundles of fine glia fibers surrounded by a rich mass of collagen fibers. The glia fibers ran parallel to the direction of the bundles, but some were intertwining. Often the glia fibers ended in feet on the vessels, or directly by collagenic fibers. Nerve cells were not present, but isolated nerve fibers were seen.

Case 6 concerned a gunshot injury of the upper parietal region, chiefly on the right, with spastic paraparesis of the legs and a bone defect. Epileptic attacks first occurred seven years after the injury. The ventricle was markedly dilated and drawn over to the bony defect. Operation revealed marked adhesions between the skin, dura and brain. The histologic examination was not complete.

Case 7 concerned a gunshot injury of the left regio retrocentralis and parietalis with sensory disturbances of the right half of the body. Epileptic attacks first occurred seven years after the injury. In the region of the bony defect there was adhesion of the skin, dura and cerebrum. The roof of the ventricle was pulled toward the bony defect. At operation mechanical pulling on the dura, which was adherent to the brain, produced an epileptic attack. The dura was very thick, and fibrous tissue strands penetrated from it deep into the brain sub-

stance. Below this invading zone of fibrous tissue was an area of softening that was limited chiefly to white matter. In this zone there was a marked increase in the vessels, and these with the vascular insertions of the astrocytes formed a rich "vaso-astral framework."

Case 8 concerned a severe birth injury of the right cerebral hemisphere with a large bone defect, penetration of a large bone fragment into the brain and a left hemiparesis. The first epileptic attacks occurred at the age of 9, and at 10 the penetrating bone fragment was removed, with cessation of epileptic attacks for seven years, followed by their reappearance. An encephalogram showed the right ventricle pulled up practically to the bone defect, and the entire ventricular system pulled over to the right. The skin, dura and brain were markedly adherent to one another. A pull on the dura, which was adherent to the brain, caused an epileptic attack. The dura and brain scar were excised and the ventricle opened widely. Histologic studies showed penetration of connective tissue into the brain from the dura. Between the dura and the brain were numerous peculiar bundles of glia fibers and astrocytes surrounded by connective tissue. The oligodendroglia showed acute cell changes.

Case 9 concerned a gunshot injury of the right occipital region, with a left hemianopia. Two years after the trauma epileptic attacks occurred. The skin, dura and brain were markedly adherent to one another. The ventricular system was pulled to the right, especially the right posterior horn, which showed a large cystlike defect reaching practically to the bone defect. The excised scar showed marked invasion of the brain by dense connective tissue fibers from the dura, below which was an area of glia fibers arranged in parallel rows and astrocytes.

Case 10 was that of a boy, aged 7, with a traumatic injury of the brain, who despite the destruction of the left retrocentral-parietal and temporal regions did not have sensory disturbances, aphasia, apraxia or difficulties in reading or writing. Epileptic attacks began four years after the trauma. The skin, dura and brain were adherent. The ventricular system was pulled to the left. A large dura-cerebral scar was removed at the operation, and its histologic structure was similar to those already mentioned.

Case 11 concerned a traumatic injury of the right frontal region, with epileptic attacks occurring four years after the injury. The lateral ventricle was pulled over to the defect, with adherence of the skin, dura and brain, and with a typical histologic picture.

Case 12 concerned a traumatic injury of the right retrocentral region, with focal sensory disturbances, and epileptic attacks occurring five months after the injury (following immediately on an osteoplastic repair of the bone defect), dilatation of the ventricle, adhesion of the skin, dura and brain, and the usual histologic picture.

Of the twelve cases reviewed, only two were without a bone defect. Particularly interesting is the fact that in many cases the interval between trauma and the first occurrence of the epileptic attacks was long, the average being five and eighth-tenths years. Among more than 100 cases of traumatic epilepsy in which operation was performed since the war, the number of cases with an interval of several years between the trauma and the epileptic attack was extraordinarily large. In this connection case 3 is of great interest. In this case there was no bone defect, and the onset of the attacks occurred eleven years after the injury.

In five cases epileptic attacks were brought on by pulling on the adherent dura, and in almost all of the cases by faradic stimulation of the brain in the region of the injury. The production of epileptic attacks by mechanical stimuli is well known. The sensitivity of the brain to such stimuli is great in many cases. Foerster and Penfield have often seen epileptic attacks produced by wiping the cortex of an epileptic patient in the removal of splinters of bone or missiles, and even in simple percussion of the skull in tuberculous meningitis, serous meningitis, meningioma and cysticercosis cerebri.

In eight cases there were no attacks following the operation. In these cases the interval after the operation varied from twenty months to five years and three

months. One patient suffered from an attack after an interval of four years and three months. One patient was free from attacks for three years, after which he had mild spells. In two cases the postoperative course was not known.

In all cases the pulling of the ventricle over to the side of the injury was clearly shown in the encephalogram. In the least marked cases the ventricle on the side of the injury was dilated and pulled toward the bone defect, i. e., the point of adhesion between the skin, dura and brain. In marked cases the ventricular dilatation assumed the character of a cystic pouch. The question arises why this pulling of the ventricular system occurs. It can be directly related to the cicatricial pull. Histologically, in all twelve cases there was a definite dural-cerebral scar, consisting of considerable collagen that had penetrated into the brain and a marked increase in the number of astrocytes around the scar, and of blood vessels in and around the wound. The scars in the cases in human beings differ somewhat from those experimentally produced. First, there are many more parallel glia fibers in the cases in human beings. This type of glial picture is found in degeneration of the posterior column and in multiple sclerosis. In the experimental animal the time is much too short for the development of such a picture. In the cases in human beings the interval between the trauma and the excision of the scar varied from seven to eighteen years. During this time a progressive destruction of brain tissue occurred. That the process is progressive is shown by the presence of pigment-laden cells around the vessels and the focal alterations in the microglia cells. In one case there occurred acute swelling of the oligodendroglia. Another difference between the experimental animal and the human being lies in the much greater destruction and disappearance of the cerebral supporting tissue in the latter. This process favors the progressive contraction of the scar, which causes the pulling over of the ventricle. The constancy of the cicatricial pull is illustrated by case 3, in which there was a definite retraction of the brain following the excision of the dural-cerebral scar.

Foerster and Penfield advocate the excision of the dural-cerebral scar in all cases of traumatic epilepsy, excising down to healthy brain tissue. In cases in which the ventricle reaches to the surface, it is opened wide. The dural defect is repaired, but no attempt is made to repair the bone defect. In cases in which the ventricle is opened, no new scar is possible, while in other cases it is a possibility.

ALPERS, Philadelphia.

MORPHOGENETIC AND ANATOMIC INVESTIGATIONS ON THE RAMI COMMUNICANTES OF THE SPINAL NERVES IN MAN. M. WREDE, Upsala läkaref. förh. **35**:223 (Aug.) 1930.

This investigation was carried out on human embryos at the Anatomic Laboratory of the University of Upsala (Agduhr). Series of embryos were used, some of which had been stained with hematoxylin-eosin and some impregnated by a silver method of Agduhr.. One embryo of 8.6 mm. had been impregnated with Cajal's method. Models were reconstructed after Born's or Strasser's methods, either in wax or as drawings on glass plates. The anatomic investigation was carried out on a dissection of the body of an adult man. Altogether, ten embryos from 6 to 19.9 mm. in length (measured after fixation in formaldehyde) were studied.

The connections between the spinal nerves and the sympathetic chain in man arise partly from branches growing from the spinal nerves toward the sympathetic chain, and partly from sympathetic fibers growing toward the spinal nerves. The first group, the rami viscerales, consists of two different categories: one that joins the sympathetic chain, and the other that runs directly to the viscera without joining the sympathetic chain. The rami viscerales of the spinal nerves may be divided into a thoracolumbar group from the first thoracic to the third lumbar nerve, and into a sacral group, from the second to the fourth sacral nerve. The rami of the first group always arise from the rami anteriores of the spinal nerves at a rather constant distance from their point of division into anterior and posterior rami. The area of distribution corresponds approximately to the area of the white rami communicantes, as it was described in man by Harman. In the embryo

6.6 mm. in length, the rami viscerales of this group are seen joining the most ventral part of the aorta. They form probably the first anlage of the nervus splanchnicus. Only in the embryo of 8 mm. have the branches to the sympathetic chain developed to the size of the splanchnic nerve anlage. The division of the visceral rami into separate fasciculi disappears more and more; finally in embryos longer than 12.5 mm., a consolidation into compact nerve fibers takes place. The rami at the first thoracic and at the first to third lumbar nerves, which are still divided into different fasciculi, form an exception to this rule. In the 10 mm. and 10.3 mm. embryos, a distinct separation of the visceral rami into a branch going cranially and another caudally was noticed. The first branch joined the sympathetic chain, while the second branch joined the anlage of the splanchnic nerve. It could not be determined with certainty whether the branch of the first thoracic nerve joined the sympathetic chain as a whole or whether it, too, formed a splanchnic division.

The sacral group develops visceral branches in the embryo of 12.5 mm. They form the anlage of the pelvic nerve. Connections with the sympathetic chain can be seen only in the embryo 16 mm. in length.

The first development of the second group of rami communicantes, those branches of the sympathetic chain that grow toward the spinal nerves, begins in the 10 mm. embryo. Two different groups are distinguished. The first group of such rami communicantes arises in the segments of the first to the sixth cervical nerves and is formed by fibers which stream to a relatively distant point of the anterior ramus of the cervical nerves. They are closely connected with the muscular branch, and it seems probable that this ramus follows the spinal nerve to the muscle.

The second group of rami communicantes, growing from the sympathetic chain toward the spinal nerve, is composed of fibers which join the segmental arteries. They accompany those arteries into the foramina intervertebralia or sacralia anteriora, respectively, and send fibers toward the spinal nerve. The latter join the spinal nerve between the point of exit of the rami viscerales and the point of division of the spinal nerve into its anterior and posterior ramus. Sometimes one may see the union of two different branches arising from the sympathetic chain. In the 20 mm. embryo a third kind of rami communicantes is described in the cervical and the upper four or five thoracic segments. They take their course in the thoracic region between the collum costae and the corresponding processus transversus, and in the cervical region between the processus costarius and the processus lateralis. The name of rami intercostotransversarii is proposed for them. They join the spinal nerve cranial to the segment in which they arise.

The following characteristics may help to differentiate between the rami viscerales of the spinal nerves and the rami of the sympathetic chain going to the spinal nerves: The first group is situated ventrally to the second group. The latter mostly joins the segmental arteries. The visceral rami originate from a well defined point of the anterior rami of the spinal nerve; if they branch off, the different branches will diverge in caudal and cranial directions. The rami originating from the sympathetic chain diverge to different peripheral points of the spinal nerve, and they usually join the nerve at the point of bifurcation into the anterior and the posterior branches. Sometimes they may join the visceral rami or the anterior branch of the spinal nerve. The possibility exists that sympathetic fibers grow along the visceral rami. But it does not appear likely that, in the cervical region, the visceral rami send fibers to the sympathetic chain. The observation of Kiss and Mihálik, that myelinated fibers are found in the rami communicantes of the cervical sympathetic, does not prove that the sympathetic chain receives fibers from the cervical spinal nerves. It means rather that a ramus communicans has joined the muscular branch of an anterior ramus of a spinal nerve.

The anatomic observations made on the dissection of an adult human body reveal a close similarity to the embryo of 19.9 mm. This correspondence is especially true for the rami communicantes that join the arteria vertebralis. They

arise partly from the medial and partly from the inferior cervical ganglion. The first group is found on the ventromedial side of the artery, the second group at the dorsolateral side. On the left side, the first group joins the muscular branch of the sixth cervical nerve and, therefore, the myelinated fibers that are described in this ramus communicans may easily be traced back to the spinal nerve.

The distribution of the rami communicantes of the dorsolumbar spinal nerves reflects likewise the conditions that are found in the embryo. The rami communicantes, arising from the anterior branch of the second and third thoracic nerves, which divide into a cranial and a caudal division, correspond to the visceral rami of the embryo; another ramus communicans that joins the spinal nerve at its junction with the anterior and posterior branch would correspond to a branch of the sympathetic chain. This comparison between the arrangement of the rami communicantes of the adult and that of the embryo is carried through for the other segments and many similarities are pointed out. Those rami communicantes of the segments from the first thoracic to the second lumbar correspond best with the visceral rami of the embryo which are connected most peripherally with the anterior rami of the spinal nerves.

The examination of the sacral rami communicantes demonstrates the presence of fibers that go from the nervi pelvici to the sympathetic ganglia. They correspond to those embryonic fibers that branch off from the visceral rami to join the sympathetic chain. These observations are contradictory to the present opinion that the sacral part of the sympathetic chain does not receive rami communicantes from the sacral spinal nerves.

WEIL, Chicago.

APHASIA FROM LESIONS OF THE INSULAR-LENTICULAR NUCLEUS. K. SCHAFFER, J. f. Psychol. u. Neurol. **40**:180 (May) 1930.

CASE 1.—T. H., a man, aged 53, had a stroke on June 16, 1929, for which he was under the author's observation until he died on July 15. The most striking disturbances were those of speech: 1. Spontaneous speech was impossible. When asked to speak, he would think for a while and, finding a word, he would perseverate; occasionally he was also paraphasic. 2. Understanding of spoken words was difficult. 3. Only monosyllabic words could be repeated. 4. Reading: Words of more than two syllables could not be read correctly; this, however, would vary; on one occasion he read T instead of L and A instead of D; on another occasion he read the entire word "status" correctly. Continuous reading was impossible. He read 170 instead of 17, and 213 instead of 235. 5. Writing: Spontaneous writing was impossible. Copying: The request to copy the letters B M T was followed by a perseveration of the letter B. 6. Calculation: $3+7=10$; $17+25=42$; $153+221=384$; $17+5=25$. 7. Praxia: He did not know what to do with a key or with a piece of soap; he was unable to hold a pencil properly, nor could he count the buttons on his trousers. 8. Attention: His attention, though readily fixed, could not be held for more than a second or two. 9. Free association of ideas: This was difficult to determine because as soon as he would begin to perform an act or to speak he would immediately stop. 10. His behavior showed that he had no insight into his condition; depression alternated with excitement; the slightest provocation gave rise to fits of crying and sighing. 11. Orientation was completely lost as to time, place and person.

Necropsy revealed an enlarged right cerebral hemisphere which on frontal section showed a tumor mass—a carcinoma distributed as follows: 1. In the right frontal lobe there was one small lesion, the size of a hazelnut, on the mesial side of the first frontal convolution on a level with the head of the caudate nucleus; this mass occupied the cortex and the subjacent white substance. 2. There was a small lesion on the surface of the pia extending to the cortex of the angular gyrus on the right side, but not invading the white substance. 3. There was a large tumor mass extending from the anterior to the posterior commissure of the third ventricle; this was the largest tumor mass and was definitely a subinsular lesion. Sections of this part of the brain at various levels showed that the

central and temporal opercular convolutions were absolutely intact. Neither the frontal nor the temporoparietal portions of the speech mechanism were involved.

So far as the topography of an insular-lenticular lesion and its relation to the question of central aphasia are concerned, this case presents no difficulties. In central aphasia the lesion must occupy the region between the areas for sensory and motor aphasia so that neither the frontal nor the parietotemporal areas of the speech mechanism are involved; in other words, the patient must have neither sensory nor motor aphasia. In the case under discussion there was no word deafness because the patient heard well though he did not always understand spoken words, nor was he absolutely speechless, as was evidenced by the fact that on one occasion he could read the word "status." Word understanding was defective in the first place, and he had difficulty in word evocation, i. e., the words necessary for expression were not at his disposal. The patient was helpless in speech, though he had no difficulty in hearing and was not completely inarticulate. That he fully realized his condition was evident by the fact that as soon as he was told that he was about to be examined he would begin to cry and make facial grimaces during which he would point to his mouth. Another striking feature in the case was the constant perseveration, which Schaffer attributes to poverty of association, which on superficial examination could have been wrongly interpreted as a dementia.

CASE 2.—A man, aged 29, with a positive Wassermann reaction of the blood and cerebrospinal fluid, noted one and a half years before admission that his handwriting was gradually becoming poorer and poorer and his speech drawling. Five days before admission, he lost consciousness for a moment; on regaining consciousness he found that he was unable to utter a word and that he had a hemiparesthesia on the right side of the body. This entire episode lasted but a few minutes, after which he remained well for three days when he again lost consciousness. This time he was unconscious for thirty-six hours during which he had generalized twitchings, and deviation of the eyes and mouth to the left. On regaining consciousness he was found to have a right hemiparesis with athetoid movements of the right upper extremity. His aphasic status showed that he was neither word-deaf nor word-mute; the tests for aphasia revealed practically the same results as in case 1, including marked perseveration and paraphasia.

Schaffer believes that in this case there was syphilitic disease of the cerebral vessels which had produced several cerebral vascular insults that resulted in disturbances in the understanding of words, without difficulty in articulation, and athetoid movements in the right upper extremity. The athetoid movements are of great localizing significance, because they are indicative of a subinsular (lenticulo-insular area) lesion which was most likely responsible for the central aphasia.

In both cases, therefore, there was no word-deafness and no word-mutism, although aphemia was present in the form of a dysarthria. In neither case was there any evidence of sensory aphasia. Both cases can be well correlated with the symptomatology of insular-lenticular aphasia as elaborated by Henschen. The perseveration in both cases is attributed by Schaffer to an embarrassment on account of disturbances in the power of free association. Central aphasia in its insular-lenticular localization is therefore not a so-called "center-aphasia"; i. e., it is neither a sensory nor a motor aphasia, but a disturbance in the conductivity of association, and may therefore be considered an associative, so-called central aphasia that may be conceived as a "conduction aphasia."

KESCHNER, New York.

STRUCTURE AND INNERVATION OF THE CAROTID SINUS OF MAN AND THE MAMMALS. NEW FACTS ON THE INNERVATION AND FUNCTION OF THE GLOMUS CAROTICUM. F. DE CASTRO, Trav. du lab. de recherches biol. de l'univ. de Madrid **25**:331, 1928.

As shown by the experiments of Hering, stimulation of the area of bifurcation of the common carotid is followed by bradycardia and a drop of arterial pressure. Drüner has suggested that the glomus caroticum represents the sensory

receptor for the excitation, but this opinion was not based on either anatomic or experimental studies. Further work on the subject has failed to show that such is the case. On the contrary, de Castro, in a paper published in 1926, has shown that sensory receptors are very abundant in the carotid sinus of several animals (rat, mouse, cat, dog) and in man. According to this, the receptors for Hering's reflex would be located in the walls of the sinus itself. This is demonstrated in the present contribution, in which de Castro gives a detailed account of the nerve supply to the carotid sinus of man and several animals (monkey, cat, dog, rabbit, rat, mouse and ox). The material was stained according to the methods of Cajal, Bielschowsky (Boeke's modification) and Ehrlich-Dogiel.

The gross morphology of the carotid sinus and the areas of localization of the nerve endings in the sinus are first described. The walls of the carotid sinus are thinner than the walls of other areas of the vessel. In the ruminants, in which there is no internal carotid, the areas of terminations of the nerves are found in the occipital artery, which takes the place of the internal carotid in these animals. The sensory nerve endings located in the walls of the carotid sinus of man and mammals are described and illustrated. According to the author, two main types can be distinguished, namely, diffuse and compact terminations. The complexity of the latter in man is remarkable. The fibers ending in the walls of the sinus are of three types: thick, thin (myelinated and nonmyelinated) and of medium diameter. The last are the most abundant.

The relation of the twigs and terminal enlargements of the arborizations with the vascular adventitia is described. The terminal enlargements are lodged between the adventitial connective tissue bundles. Indeed, their shape is in many cases the result of adaptation to the interstices between the connective tissue fibers. In many instances the enlargements have crescentic shape and are applied against the nuclei of the connective tissue cells. From these facts, the author concludes that the stimulation of the nerve endings is purely mechanical and takes place through compression of the terminal enlargements by the adventitial collagen fibers during vascular dilatation. Destruction of the nerves of the region by means of phenol suppresses or markedly interferes with the "sinus reflex."

The second section of the paper deals with the centripetal system of the vessels of the glomus caroticum and the probable function of the latter. The arteries of the glomus are innervated by a centripetal system of great complexity. While there are some fibers of vagus origin, most of the fibers of the system are derived from the glossopharyngeal, which also furnishes the receptors of the carotid sinus. The bundle of fibers supplying the sinus and glomus constitute the "intercarotid" nerve (de Castro), which corresponds to the ramus caroticus glossopharyngei of Breuecker, and the "Sinusnerv" of Hering. In the glomus the fibers of the intercarotid nerve are distributed over the arteries and arterioles, which are derived from the external carotid or the occipital artery (ruminants). The terminations of these fibers are sensory and appear as diffuse arborizations located in the adventitia of several contiguous vessels. In addition, the vessels of the glomus are supplied with vasomotor fibers belonging to the autonomic nervous system. The trophic centers (neurons) of the vasomotor fibers are not located in the sympathetic chain, since the fibers persist after extirpation of the cervical sympathetic. They are the axons of the neurons of the small ganglia of the glomus. Section of the glossopharyngeal does not cause degeneration of the whole centripetal system; the same is true when the vagus and ganglion nodosum are resected. Injection of Ringer's solution under pressure through the carotid after destruction of the nerves to the carotid sinus causes a slight fall of the blood pressure and slows the heart rate. De Castro thinks that this depressor action is due to stimulation of the centripetal system of the vessels of the glomus. Besides the centripetal fibers ending on the arteries and arterioles of the glomus, the parenchyma cells of the latter are in contact with numerous nerve endings, which were at first regarded as secretory by de Castro. However, further experiments have shown that the nerve endings mentioned also belong to centripetal fibers reaching the glomus through the "intercarotid" nerve. Intracranial section of the glossopharyngeal vagus and accessory nerves in cats and dogs does not cause degeneration

of the arborizations ending on the glomus cells. The same is true of the nerve endings of the arteries and arterioles. According to this observation, the trophic centers (neurons) of the fibers of the centripetal system of the glomus are located in the ganglia of the glossopharyngeal and vagus, which contain monopolar cells of sensory type. On the other hand, if the cervical sympathetic is destroyed in animals in which intracranial section of the glossopharyngeal and vagus has been carried out, the nerves of the glomus do not degenerate, a further proof of their centripetal or sensory nature.

From these facts de Castro concludes that the glomus caroticum is neither a paraganglion nor a typical endocrine gland. It rather represents a special sensory organ the function of which is, perhaps, to receive certain qualitative modifications of the blood. Each parenchyma cell of the glomus theoretically possesses two poles: one, directed toward the blood, is in intimate connection with the sinusoidal capillaries of the glomeruli, and it seems to contribute to the formation of the capillary wall; the other, the nervous pole, is in contact with the terminal nerve fibers. The glomus does not represent the anatomic basis of the carotid reflex. The receptors for the latter are located in the walls of the carotid sinus.

NONIDEZ, New York.

IS HEADACHE OF PURELY NASAL ORIGIN FREQUENT? GIORGIO FERRERI, Rev. d'oto-neuro-opht. **7**:631 (Oct.) 1929.

In the last analysis, headache, whatever its mechanism of origin, whether caused by anemia or hyperemia, is always a disease of the meninges. The facts that it is accentuated toward evening, that it disappears in the morning when equilibrium of the circulation is reestablished, and that it is influenced by positions of the body which provoke congestion or ischemia of the head prove its origin to be most frequently circulatory. Headaches that are not dependent on morbid intracranial states but on auricular, ophthalmic and nasal lesions behave in this manner. When the rich nerve supply of the mucosa is considered, it is not surprising that the nose can be the point of departure of headaches. Peripheral stimulation of the sympathetic fibers in the nose causes local alterations of the dural and pial circulation, with consequent variations in pressure and headaches. The anterior carotid sympathetic system reaches the nasal mucosa by the sphenopalatine ganglion. To this system is opposed the posterior cervical sympathetic nerves, which pass along the vertebral artery and are grouped into the vertebral nerve and reach the meninges and the choroidal plexuses. Almost all of the parasympathetic fibers come from the nuclei of the eighth and ninth nerves and, uniting, form the great and the small superficial petrosals. These connect with the carotid sympathetic by means of the vidian nerve, which goes to the sphenopalatine ganglion and thence to the nose; others go to the orbital branch of the fifth nerve. To this is added the rich nervous network of fibers from the fifth nerve, all intricately intermingled. It offers an important pathway for stimuli and reflexes from distant organs and is a principal factor in the determination of several forms of nasal pathology.

Headaches of nasal origin constitute three groups: (1) those due to recognized lesions of the nasal accessory sinuses; (2) those of nasal origin proper or those due to factors that act on the mucosa, as spurs, ridges, etc., and (3) "permanent" headaches which are dull, are localized around or in the skull, are constantly in the same region and are true cephalalgias. The first type is frequent; the "permanent" headache of purely nasal origin is rare. The second type of purely nasal origin is said to be due to nasal stenosis, causing stagnation of secretion and blocking of sinus drainage, to malformations of the septum and turbinates, to chronic inflammation of the mucosa, to chronic edemas of toxic origin, to allergic and anaphylactic trouble or to endonasal tumors. The author's experience, however, in these cases has almost always been disappointing, because of the negative results of nasal therapy. Usually the headaches have been of central or general origin and allied to the nose by the complex autonomic and sympathetic pathways and by

the sensory trigeminus. Often a headache that seems of a purely nasal type is only a symptom of a toxic state, cardiovascular or hepatic, and the rôle of a disturbed menstrual cycle must not be forgotten. Just as the nose may be a point of departure for headache by the centripetal pathways, so can distant disturbances act on the nose by the centrifugal pathways.

Two illuminating cases, which were thoroughly studied, are recorded. In case 1, a girl, aged 18, had suffered with generalized headaches (more severe in the frontal region) for two years. All possible examinations were made and gave negative results, which led to the conclusion that an endonasal cause (septal ridge which compressed the middle turbinate) was responsible. This was reenforced by the fact that the application of cocaine to the nose gave relief at first. Resection of the nasal septum and cauterization of the turbinates completely failed to relieve the headache. Some months later, pain in the right shoulder directed attention to the liver, and cholecystitis was discovered. Proper treatment relieved the condition, and the headache disappeared. Case 2 concerned a young man who had suffered with severe headaches for six months. They appeared in the mornings, especially in the forehead, and radiated to the region between the pharynx and the eyes. All examinations, including roentgenograms of the head, gave negative results, except that an enormous septal deviation with hypertrophy of the turbinates was found, which almost completely abolished nasal respiration. Resection of the septum and a turbinotomy did not relieve the headache. A second series of examinations with repeated urinalyses revealed a recurring inflammation of the kidney, which was treated, with great relief from the headaches.

Everything considered, given the enormous number of sufferers from headaches and the great number of persons with deviations, spurs and malformed turbinates who have no headache, the author concludes that headache caused solely by endonasal conditions is really very rare, at least in Italy. According to foreign writers, this is not true in other countries, and the suggestion is made that great weight must be given to geography, climate, environment, mode of living and especially race as etiologic factors.

DENNIS, Colorado Springs, Colo.

THE RELATION OF THE VISUAL AREA AND THE VESTIBULAR APPARATUS. HANS HOFF, Ztschr. f. d. ges. Neurol. u. Psychiat. **121**:751, 1929.

Brunner and Hoff have found a relation between the vestibular apparatus and the visual zone. They assume that in the region of the gyrus angularis and adjacent territory there is a zone that sifts stimuli from the vestibular apparatus. These stimuli are for the most part suppressed and compensated for by ocular movements, and only a few pass beyond the region of the sulcus interparietalis into the visual sphere. Hoff reports two cases in which it was possible to study these relationships more closely. The first case, from which most of the inferences are drawn, was that of a man, aged 36, who had sustained a trauma to the head in falling from a car. He was unconscious for four weeks, and was operated on in order to remove some splinters of bone from the skull. Four years later, he developed jacksonian attacks in the left arm and leg. Later, he developed generalized attacks, which were preceded by an aura in which he saw objects about him as if through a cloud and as if they were frayed and flattened out from above downward and from side to side. A year later, he developed a left hemianopia for all colors, with retention of white and black. He still experienced the delusion that objects were frayed, and he had a constant feeling of anxiety that anything passing into his blind field was approaching its doom. Organically, he showed a horizontal nystagmus, difficulty in ocular movements to both sides, and paresis of the left side with a Babinski sign. Two years later, he showed a complete left hemianopia, with the presence of marked light waves in the hemianopic field and with a constant nystagmus to the right. Epileptic attacks were frequent and were preceded by an aura in which he saw

waves in the hemianopic field. These waves consisted of broad, light and dark layers filling the entire hemianopic field and in constant motion. During this aura the eyes were fixed to the right. Then a coarse nystagmus to the left suddenly developed in the eyes, until they were in left deviation. At this point the optic phenomena disappeared, and the attack appeared. The patient never lost consciousness. After an attack he asserted that he did not know left from right, although he could tell an upper from a lower position.

The bony defect in the skull lay over the gyrus angularis. When the skin was cooled over this area, a visual aura of waves was precipitated in the hemianopic field. The labyrinths showed hyperexcitability on both sides. Stimulation of the right ear caused the onset of an attack. Hoff assumed that there was scar formation over the right gyrus angularis, possibly with cyst formation, compressing or destroying the optic radiations. Operation revealed a superficial cyst of spinal fluid exactly over the gyrus angularis, extending for a depth of 2 cm. into the brain. The cyst was emptied, and the patient left the hospital. Four weeks later attacks again developed, with the distortion of objects as in the beginning of the disease.

Hoff calls attention to the concept of Pötzl that the stimuli which come to the cortex from deeper centers are distributed by the gyrus angularis. Disease of this region is followed by a penetration of the stimuli into deeper-lying centers and the occurrence of an epileptic attack. The color hemianopia is difficult to explain. The work of Wilbrand and Saenger and of Lenz and Pötzl shows that the basal portions of the visual area and the basal part of the optic radiation is responsible for the perception of color. The occurrence of hemianopia for colors, therefore, with a superficial lesion such as was found here, must be due to transverse fibers in the gyrus angularis between this area and the basal part of the visual area.

Hoff asserts that the gyrus angularis sponges up the stimuli of deeper centers and distributes them in the cerebral cortex. Disease of this area causes a lowering of threshold, and the occurrence of epileptic attacks with rotation of the head and deviation of the eyes toward the direction of the injury. Part of the function of the gyrus angularis also is to unite the haptic functions into a unified whole. Disease of this region is responsible, therefore, for an inability to recognize sides, and an inability to cross the midline. The gyrus angularis, moreover, protects the visual area from the stimuli that are conducted to the cortex from the vestibular area by suppression of these stimuli. The loss of this function permits the penetration of vestibular stimuli into the undefended visual area, and the occurrence of visual waves is an equivalent of the later oncoming nystagmus.

ALPERS, Philadelphia.

HEADACHES AND VASCULAR SPASMS IN OPHTHALMOLOGY. BEAUVIEUX, F. PIECHAUD, and RUDEAU, Rev. d'oto-neuro-opht. **7**:619 (Oct.) 1929.

Vascular spasms in the cerebral domain can entail the phenomena of headaches when they occur in the ocular globe or in the cerebral visual centers.

Retinal Vascular Spasms: When ophthalmologists report the clinical picture of retinal spasm, they emphasize the functional visual disturbances but say little about the sensory troubles of the patient. Two cases are reported. One occurred in a woman, aged 53, who during the previous years had experienced numerous attacks which began with sudden violent frontal headache and progressed with loss of vision, the entire crisis lasting about fifteen minutes. The vision then would slowly return. Although the Wassermann reaction was negative, antisyphilitic treatment had been used, without benefit. The second case illustrates the fact that the headaches may not always be so severe or frequent. A man, aged 46, suddenly noticed a visual disturbance that he compared to the effect of looking at the sun. He soon became blind and remained so for eight hours. He said that he had not had headache, but that he had the sensation of having been changed and of not being himself. The ocular symptoms improved in forty-eight

hours, but his mental state remained so disturbed that he felt unable to resume work. It is true that this man had no real pain, but his intense and prolonged cerebral trouble can be allied to certain headaches.

Cortical Vascular Spasms: While fugitive, these spasms can entail headaches of varied kinds. The author asks, "Is it possible to eliminate completely from the headaches the migrainous syndrome and ophthalmic migraine?" Monbrun explained the hemianopic ocular disturbances by a simple spasm of an arterial branch to the visual zone while the painful manifestations, accompanied by scintillating scotoma of irritative origin from cortical hyperfunction followed by exhaustion of this cortex, would be due to simultaneous spasm of the venous and arterial circulation of the zone involved. In order that the spasm of the cortical visual zone would entail symptoms of migraine, a venous spasm must be added to the arterial. Perhaps, also, there must be a more extended localization—to the sensory cortex of the temporoparietal region—by a combined spasm of the posterior cerebral and the sylvian vessels.

Four case reports are given. A woman, aged 57, had had difficulty in looking to the left for some time. The arterial tension was 13/8½ (Pachon). A lateral left homonymous hemianopia was established on Dec. 20, 1927. Vision in the right eye was 1 with +0.5 glass; in the left eye, it was normal. The pupils, pupillary reflexes, eyegrounds and ocular muscles were normal. There was improvement in vision during the following five days. A violent right-sided headache appeared on January 10, followed by a left hemiplegia.

Signs of migrainous headaches only rarely accompany hemianopias or hemiachromatopias. The headache is often replaced by a heaviness or by cephalic disequilibrium.

The following case is typical of hemianopic migraine. A man, aged 48, had suffered for some years with marked diffused headaches. On Jan. 19, 1929, he was seized suddenly with an atrocious migraine accompanied by scintillation and flashes of light in the right visual field, which was soon replaced by a thick fog. There existed also a state of obnubilation of the intellectual faculties. The papillae were found to be somewhat pale, and there was contraction of the retinal arteries. Visual acuity was 10/10. There was a right homonymous lateral hemianopia, almost complete, and a mild degree of aphasia with word blindness and deafness. There was no disturbance of peripheral motion or sensation. The blood pressure was elevated, 22 systolic and 13 diastolic. These troubles were ameliorated by February 7, but the headache persisted. This was not a true ophthalmic migraine, but approached this syndrome.

These observations exemplify all the nuances of algic phenomena accompanying spasms of the branches of the posterior cerebral and sylvian vessels, from the simple sensation of intracerebral tension and of heaviness of the head to veritable migraine accompanied by classic scintillations.

DENNIS, Colorado Springs, Colo.

THE INTERESTS AND IDEALS OF BRAZILIAN CHILDREN. HELENE ANTIPOFF, Arch. de psychol. **22**:153 (Feb.) 1930.

In order to study children's interests, a questionnaire was submitted to 760 children whose ages ranged from 10 to 14 years, but who were in the same grade in school. The replies were analyzed as follows:

1. What kind of school work do you like best? Arithmetic and Portuguese were the most preferred subjects, 33 per cent of the boys and 28.5 per cent of the girls preferring the former, 13 per cent of the boys and 23.5 per cent of the girls, the latter. The author does not think that this preference is due to the fact that the child is more proficient in these subjects, for previous studies have shown that children may prefer certain studies and yet do poorly in them, but because the newer teaching methods employed in these subjects make them more intelligible and interesting than do the methods employed in the others.

2. What work do you like to do at home? More than a third of the children of both sexes preferred housework. Many more boys than girls preferred gardening, looking after pets, etc. Very few children expressed any preference for reading.

3. What game do you like best? Eighty-five per cent of the boys preferred active sports, 68.9 per cent preferring ball (football).

This result coincides with those found by other investigators in other parts of the world. Interest in reading, stamp collecting and constructive toys (mechano sets) was much less common than has been found in other countries. Some of the interest in sport may have been due to the season of the year at which the questionnaire was answered. Forty-five per cent of the girls preferred active sports, 39 per cent imitative play, and 21 per cent preferred dolls only.

4. What would you like to receive for your birthday? The boys expressed a high degree of preference for apparatus for games, balls, bugles, etc.; the girls, a preference for clothes, ornaments and dolls. Books occupied the fourth place in the boys' preference, the second in the girls'.

5. What would you do if you had lots of money? A third of the boys and more than a third of the girls would make donations for charitable or religious purposes. Twenty-five per cent of the boys and 18 per cent of the girls would invest it. Only a small percentage would use it for amusements or to buy things for themselves.

6. What do you wish to be when you grow up? Although the majority of the children came from modest homes, 51 per cent of the boys and 70 per cent of the girls chose a professional occupation — engineer, physician or lawyer for the former, teacher or pianist for the latter. Only 22 per cent of the boys and 17 per cent of the girls chose manual occupations.

7. Why did you make that choice? The majority of the children gave vague answers — I like it; it is a good occupation, etc. Ten per cent of the boys and 4 per cent of the girls made the choice because of the remuneration, and a similar number because it was honest.

8. What person would you like to resemble? Nearly half of the group selected a member of their own family as an ideal. This differs from the results of similar enquiries among children of the same age in other countries. The author thinks that the closeness of the family group in Brazil tends to keep the child immature and produces this result.

9. Why do you wish to resemble this person? The largest percentage of choices was made on the basis of moral qualities; the next on intellectual or physical qualities, and the third largest on understandingness.

10. What book do you like best? By far the largest percentage of the children preferred fairy stories. Histories, adventures and school books were preferred next. The author believes that this indicates that the Brazilian child compares unfavorably in matureness with children of other civilized countries. One reason for this may be the shorter time the former actually spends in school.

PEARSON, Philadelphia.

THE PATHOLOGIC ANATOMY OF EPILEPSY: FIRST PART: INTRODUCTION AND MATERIAL: PATHOLOGIC ANATOMY OF THE EPILEPTIC ATTACK. M. MINKOWSKI, Schweiz. Arch. f. Neurol. u. Psychiat. **25**:179, 1930.

Since gross anatomic lesions are found in the brains of those who have had "genuine epilepsy" for years, and constitutional factors seem to play a rôle in symptomatic epilepsy, Minkowski believes that one should make a clinical distinction between the two only in the sense of whether or not there is a history in the individual case of factors that could produce epileptic seizures or their equivalents. In this portion of his study the author reviews his observations on

the brains removed from eight patients dying of status epilepticus or from other causes in or shortly after a typical epileptic seizure. Sections made from blocks including the tissues about the lateral, third and fourth ventricles as well as from different portions of the anterior central and first frontal convolutions and the angular gyrus were prepared with hematoxylin-eosin and van Gieson's and Nissl's stains.

In general, the observations agree with those reported by other observers. Acute chromatolytic changes in the Purkinje cells with corresponding glial proliferation were found as described by Spielmeyer, but the cellular alterations described by that author in Ammon's horn could not be confirmed. Spielmeyer, however, found such changes in but one sixth of the patients dying in status epilepticus. In only one of Minkowski's cases did the Betz cells of the cortex show anything significant.

Fresh vascular changes, including dilated vessels filled with fresh clots, perivascular spaces distended mostly with amorphous material but occasionally containing cellular elements (mostly round cells), and hemorrhages both in the perivascular spaces and in nervous tissue were found in all cases. Although these changes were diffuse, they showed a predilection for the subependymal tissues, the cerebellar nuclei and the leptomeninges. In part of the cases the vessels of the choroid plexus were similarly affected. The author searched carefully for hyaline thrombi, but found them only occasionally. The cells of the choroid plexus and ependyma showed changes some of which appeared to be acute. In a few cases there were extensive adhesions between the choroid plexus and the ventricular wall in the inferior horns of the lateral ventricles.

Because of their constancy the author regards the vascular changes as significant even though they have been described in other conditions. He does not think that they can be explained on the basis of compression of the veins of the neck during the seizure, because in death from suffocation such alterations are not found in the brain in spite of multiple hemorrhages elsewhere. In two of the cases in which death was due to suffocation during the seizure, the characteristic observations were less pronounced than in the others. The vascular stasis described could well have followed a primary vasoconstriction, as believed by some; the author himself believes that vasomotor phenomena are an important feature of the epileptic attack although not the primary cause, and he does not think that the alterations in the nerve cells could be due to ischemia alone. He points out further that his material is obtained from severe cases and that in an ordinary seizure the changes are probably slighter and of a more or less reversible nature.

In the second part of his study, which is to appear later, tissue changes of a chronic nature will be described and the fundamental cause of epilepsy considered.

DANIELS, Rochester, Minn.

TUMOURS OF THE PINEAL, CORPORA QUADRIGEMINA AND THIRD VENTRICLE: THE INTER-RELATIONSHIP OF THEIR SYNDROMES AND THEIR SURGICAL TREATMENT. MARK ALBERT GLASER, Brain **52**:226 (July) 1929.

Symptoms and clinical signs of tumors of the pineal body, corpora quadrigemina and the third ventricle are closely interrelated and may simulate one another. At present it is not justifiable to attribute sexual precocity to a manifestation of endocrine disturbance of the pineal body. When it is present, a pineal tumor is to be considered as most probable; without it, however, a pineal tumor cannot be excluded. The initial symptoms in all of the cases here considered were those of increased intracranial pressure, such as headache, nausea and vomiting. Choked disks were present in all but one of the cases.

Involvement of the ocular apparatus was by far the most important objective sign. Neither the ninth, tenth, eleventh or twelfth nerves were involved, but the other cranial nerves occasionally showed signs of some encroachment. In three fourths of the cases the motor system was affected either in the form of a

unilateral or bilateral paresis or paralysis. Seven patients presented signs of cerebellar involvement.

Each patient showed one or more signs of ocular disturbance. The most important diagnostic observations, and one which occurred more frequently than any other in these tumors, was an involvement of the pupillary reflex arc. Failure of reaction to accommodation occurred in eight patients, and in three it was sluggish. Failure of reaction to light occurred in two patients. Five had incomplete and two had definite Argyll Robertson pupils. Dilated pupils were present in ten of twelve patients. Irregular pupils occurred in five, and unequal pupils in three patients. Restriction of ocular movement was present in ten patients and consisted of the following defects: failure of outward movement of the eyes in three, failure of inward movement in two, internal strabismus in two, limited upward movement in one and unliateral upward displacement of the eyeball in one. A failure of conjugate movement of the eyes upward above a horizontal plane cannot be considered pathognomonic of tumors of the pineal gland, but is rather an evidence of involvement of the midbrain.

Signs of cerebellar involvement are frequently present in this group of cases and often lead to a false suspicion of a tumor in the posterior fossa. The chronology of the history is of extreme importance in differentiating the lesions considered from those in the posterior fossa. Tumors involving the midcentral region present cerebellar signs late in the course of the illness, whereas primary cerebellar tumors give these characteristic symptoms early. Ventriculograms and ventricular estimation may give valuable data for the differentiation of midcentral tumors from those of the posterior fossa, as well as to differentiate midcentral tumors from each other. Vestibular tests are suggested by the author to give valuable information in the diagnosis of the neoplasms under consideration. This will be treated in a paper to be published by him. Surgical intervention is to be attempted in all cases. Emphasis is placed on the value of the frontal incision through the dilated lateral ventricle and the foramen of Monro to the third ventricle.

BECK, Buffalo.

TRANSIENT HEMIANOPIAS IN ANGIOSPASM. BEAUVIEUX, Rev. d'oto-neuro-opht. **8**:94 (Feb.) 1930.

Two cases, almost identical, are the basis of this study. A man, aged 68, had suffered from generalized arteriosclerosis with slight hypertension (20 systolic and 14 diastolic) and intellectual torpor for some months. At times he complained of tingling in the legs and a sensation of cold accompanied by a mild asphyxia. In November, 1928, he had a sudden, violent headache and lost consciousness. This was succeeded by a sensation of rays of light and sparks in the eyes lasting several hours, following which objects were seen through a scintillating fog. Examination, two days later, revealed a classic right lateral homonymous hemianopia, total for white and colors, with conservation of central vision. There were no aphasia, verbal deafness, blindness or trouble with the memory. In three weeks the hemianopia had completely disappeared, leaving only some difficulty in fixing objects, which made reading and writing troublesome. Case 2 showed verbal deafness and blindness and aphasia in addition to the hemianopia. In both cases there was a transient lesion in the visual radiations or the cortical centers which left no lasting alteration of the nerve elements. Only ischemia in some part of the visual pathways can explain this picture. A spasmodic contraction of the arterial walls was the probable cause in these cases.

The onset with sudden intense headache, followed almost immediately by symptoms of cortical irritation, reminds one of ophthalmic migraine. The cases are curious from the long duration of the perimetric symptoms, but similar observations have been reported by Monbrun and Di Marzio without sequelae of lasting lesions of the nerve elements. Since such damage occurs after the cells are deprived of nutrition for only a few hours, it is probable that the actual spasm lasted a very short time and that a secondary functional torpor followed, which perhaps spread

to contiguous territory. The prognosis must be reserved until it is determined whether the ischemia is due to spasm of the vessels or to a thrombus. The treatment is by antispasmodic medication: atropine, amyl nitrite, etc.

According to Monbrun, each hemisphere presides over the corresponding half of the retina: the left over the temporal half in the left eye and over the nasal half in the right eye. At their posterior part the visual radiations are divided by the occipital cornu of the lateral ventricles into an upper and lower bundle. The upper bundle contains fibers from the two superior quadrants; the left hemisphere receives fibers from the superior temporal quadrant of the left eye and the superior nasal quadrant of the right eye. In the same manner the inferior quadrants send fibers to the hemisphere through the lower bundle. The anterior retrolenticular segment of the radiations is supplied by the anterior choroid artery, the middle portion is supplied by the sylvian artery and, in the posterior portion, the upper bundle receives branches from the sylvian and the inferior from the posterior cerebral artery. At their terminations in the calcarine fissure, the posterior cerebral artery supplies the whole of the optic centers. In case 2 the spasm was probably in the sylvian artery supplying the upper bundle in the radiations, while in case 1, which had no sensorimotor sensitivomotor syndrome, the spasm was in the left calcarine artery.

DENNIS, Colorado Springs, Colo.

CIRCULATORY DISTURBANCES AND PSYCHOSES. W. SPIELMEYER, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:536, 1930.

The changes in the brain in the "circulatory psychoses" are of two types: (1) focal changes without general changes and (2) general changes in the cortex with more or less focal injuries. In the latter type there are small erosions and scars in the cortex and subcortex, and more or less striate-like losses of cells in the upper half of the cortex. In all these changes, arteriosclerotic and embolic causes have no part. They are caused by disturbances of circulation: decompensated hearts, cardiac insufficiency and similar causes. The question arises in how far these changes are responsible for the psychosis. A study of brains of mentally normal people shows that similar conditions can be demonstrated. Like other organs — the liver, the kidneys and the spleen — the brain is also affected by circulatory changes. The cortex shows fresh pallor in areas in cases of prolonged death, or in gradually increasing cardiac insufficiency. The same changes that one sees in the skin in the agonal stages occur also in the brain. Spielmeyer records a number of instances in which there was focal cortical pallor. He found such areas in many instances without any evidence of vascular occlusion. In no case was there vascular disease. Similar changes were found in cases of hypertension, eclamptic uremia, chronic pseudo-uremia, puerperal eclampsia, pertussis eclampsia, cerebral palsy of childhood, pantopon poisoning, in death from narcosis, and in poisoning from carbon monoxide.

These observations have no significance in diagnosis. The same changes are found in trauma as in poisoning from carbon monoxide, and the same in narcosis from chloroform, hypertension, pseudo-uremia and eclampsia. They differ only in intensity and age. These changes have no differentiating value. Their virtue lies in disclosing the common denominator in all these etiologically and clinically different diseases. This is the presence of central circulatory disturbances in cerebral injuries, referable to the most varied causes — trauma, poisons, infections and eclampsia. Similar changes are found in normal brains. They are present also in conditions in which other processes hide the circulatory troubles, as in Lissauer's type of paralysis. Furthermore, there are diseases in which changes due to circulatory disturbances are in no way the cause and expression of the essential disease process, but are only the effect of a definite pathophysiologic event, as in epilepsy.

Moreover, certain events in a clinical course can produce anatomic pictures which have nothing to do with the fundamental pathology. Such are severe psychomotor excitements. These can produce a disturbance in the circulation, and

according to v. Braunmühl, lead to acute necrobrioses in the brain. Spielmeyer shows cases with histologic pallor in the cortex in cases with excitement, and believes that the histologic pictures can be correlated with the excitement, due to the collapse of the heart function and the vasomotor apparatus.

ALPERS, Philadelphia.

THE JAPANESE ILLUSION AND THE POSTURAL MODEL OF THE BODY. ELMER KLEIN and PAUL SCHILDER, J. Nerv. & Ment. Dis. **70**:241 (Sept.) 1929.

The Japanese illusion occurs when, with arms crossed, the hands are clasped thumbs down and turned thumbward until they point upward. With the fingers in this posture, it is frequently difficult and at times impossible to move a finger indicated by another person, erroneous movements occurring more often in the finger symmetrically opposite. The error is greater on the left side, as a rule, than on the right. With the eyes open the error is more pronounced than with the eyes closed, and Burnett has concluded that the illusion lies in the visual and not in the kinesthetic experience. The illusion tends to disappear when active movements of the fingers occur. It is probable that knowledge of the body is not built up of single sensations but of shaped pictures of the body as a whole, and this postural model built up of different levels is expressed typically in the fantoms of those who have lost one extremity. Goldstein and Gelb have shown that persons with impaired optic perceptions have only a vague knowledge of their bodies, if they do not make movements. As a rule, one gets the best knowledge of his body when in contact with external objects. If an unusual or abnormal position of the limbs is maintained, the person tends to neglect it and to experience the normal position in spite of data furnished visually.

The authors experimented on each other and on three other subjects. In none of the experiments were mistakes made when the finger was touched, but all of the subjects had an increased feeling of strangeness in mistakes made in response to the pointing order. Verbal orders and self-given orders seldom provoked erroneous movements. Mistakes in movements of the thumb and the fifth finger were rarer than with the other fingers, while the fourth finger was especially subject to failure. The scheme of the hand as represented in visual imagination yields the impression of a heavy mass which feels alive, but which indicates that the passive extremity yields an incomplete picture without the changing external stimuli. Thus in daily life the visual perception of the body gives a sharper outline to the postural model than the vague knowledge obtained from the kinesthetic senses. The authors conclude that in the background of the conscious reactions, complicated psychologic processes go on, based on the total experiences of the individual, and every single experience brings into operation differentiating and integrating processes. These processes take place only if one is in contact with a changing reality, or if one receives changing impressions through vision, touch or movement.

HART, Greenwich, Conn.

ENDOCRINOLOGY AND NEUROLOGY. PETER BASSOE, Endocrinology **14**:145 (May-June) 1930.

This article is the presidential address at the fourteenth annual meeting of the Association for the Study of Internal Secretions. The author summarizes the progress of endocrinology, noting particularly the value of insulin in psychiatry in the treatment of undernourished and depressed patients. He calls to mind the occurrence of convulsions and coma in cases of adenoma of the islands of Langerhans. He points out the frequent occurrence of endocrine symptomatology, particularly diabetes insipidus, and adiposis with general atrophy following epidemic encephalitis. It is of interest to note that the basal metabolic rate is increased in a marked percentage of cases in chronic parkinsonian encephalitis and during paralysis agitans. Occasionally such patients are operated on for hyperthyroidism.

The author reports four cases. In case 1, a woman, aged 52, presented a paralysis agitans syndrome following an injury of the head. A hyperthyroid syndrome following the trauma also developed. The second patient, a woman, aged 28, presented a parkinsonian syndrome with hyperthyroidism, but with no history of trauma or acute encephalitis. The condition was diagnosed as chronic epidemic encephalitis. The patient had shown obesity, tremor and subsequently loss in weight and an increased metabolic rate. The author believed that these were the results of an endocrine disturbance. Case 3 is that of a woman, aged 52, with a depressive confusional psychosis, without signs of organic disease of the brain. She had had multiple lipomas for years, but during this period they had rapidly increased in number, size and tension. The mental symptoms were improved, and there was a reduction in the size of the lipomas following treatment with a compound solution of iodine. Case 4 is that of a man, aged 30, who had shown some gain in weight, complained of polyuria and polydipsia, and at the same time showed some mental disturbance as evidenced by talkativeness. In this man, symmetrical lumps appeared over the zygoma and on the neck. These areas were edematous and felt hot to the patient. There was a persistent glycosuria. The lumps were found to be fat. Neurologic examination gave negative results except for ataxia and weakness of the left arm. These symptoms are explained on the basis of an encephalitic lesion in the interbrain affecting the vegetative centers. The author believes that a study should be made of psychic reactions to the administration of endocrine preparations containing known hormones, of endocrine conditions with definite psychoses and of psychic conditions with definite endocrine disturbances.

WAGGONER, Ann Arbor, Mich.

HEADACHE IN CEREBRAL AND CEREBELLAR ABSCESS OF OTITIC ORIGIN. GEORGES PORTMANN and HENRI RETROUVEY, Rev. d'oto-neuro-opht. **7**:627 (Oct.) 1929.

The symptomatology of otitic abscess of the brain corresponds imperfectly to the classic picture of abscess of the brain of other origins. However, headache is of considerable relative frequency and is of prime diagnostic value. It occurs with other intracranial complications of otic suppurations: extradural abscess and meningitis. Ten cases of otitic abscess of the brain have been studied with reference (1) to the peculiar character of the headche, its localization, intensity and the differentiation from other endocranial complications, and (2) its symptomatic value with respect to that of other classic cardinal signs.

In general, headache from extradural abscess is slight—a heaviness of the head localized in the temporal or parietal region of the affected side. Localized serous meningitis causes more severe headache, while in diffuse meningitis headache begins suddenly and soon attains a violent character. Light and noise accentuate it, and although it may, at times, be localized, it is more often diffuse. In the beginning, the headache of abscess of the brain is of moderate intensity, a sensation of fatigue or heaviness or constriction, and is intermittent. Insidiously it grows worse and calls forth groans and complaints rather than the screams caused by meningitis. It is increased by movement or effort; certain positions of the head modify it, but it never remits.

Headache was present in nine of the ten cases studied, and was intense. It is a valuable sign when provoked by percussion and when constant on repeated examinations, but this sign is rare. The seat of the headache corresponds to the location of the abscess as a rule, but not always. In temporosphenoidal abscess it is usually parietal, and is occipital in cerebellar abscess. The duration varies from a few days to several weeks. It is an early symptom and is more frequent than other signs of intracranial hypertension.

Emaciation of varying degree is frequent in abscess of the brain, but to be of real diagnostic value it must be rapid. Lumbar puncture showed a predominating lymphocytosis. Localizing signs were inconstant, especially in cerebellar abscess.

DENNIS, Colorado Springs, Colo.

STATIC HYPOTONIA: A CLINICAL AND GRAPHIC STUDY OF MUSCULAR SYNERGY AND STATICS IN HYPOTONIA. T. ALAJOUANINE and M. GOPCEVITCH, Encéphale **25**:265 (April) 1930.

Reviewing the topics of muscular action in the normal subject, it is pointed out that the muscles may be divided into two series: (1) those of the antigravity group (essentially posterior or dorsal), and (2) those with the function of intermittent equilibration (essentially anterior or ventral). Then follow the experimental observations. The subject is placed in a standing position, with heels together and toes separated, and examination of the different muscular groups takes place; this is repeated with the heels separated about 15 cm. Finally, the effects of closing the eyes are investigated. Normally, a "swelling" appears about the instep, which on palpation yields a certain elasticity; likewise certain observations in the palpation of the quadriceps, in the lumbosacral muscular mass, etc., are made. The authors found that varying types of disturbances could occur: 1. Unilateral hypotonia without disequilibrium. These groups may be found in certain cases of cortical or subcortical hemiplegia, without contracture and with a minimum of pyramidal signs; in some unilateral cerebellar syndromes; in peripheral vestibular diseases after the disappearance of the vertigo; in unilateral chorea, and in unilateral attacks of the anterior roots or mixed nerves. Typical observations in this series consist of effacement of the prominence of the instep of the affected leg, a lateral mobilization of the knee cap and an increase in the compressibility of the quadriceps. 2. Unilateral hypotonia with disequilibrium. Such groups occur in vestibular lesions accompanied by the phenomena of vertigo, in cerebellar hemiplegia, in certain unilateral cerebellar syndromes and in tumors of the cerebellum. 3. Bilateral hypotonia without disequilibrium. Their groups obtain in some of the sequelae of acute anterior poliomyelitis, in polyneuritis, in certain cases of multiple sclerosis and in Friedreich's ataxia.

The second part of the article consists of a study of the footprints shown in various hypotonic conditions, with plates illustrating the effects of hypotonia and disturbed equilibrium.

ANDERSON, Los Angeles.

BASAL METABOLISM AND GASTRO-INTESTINAL FINDINGS IN EPILEPTIC PATIENTS. T. K. DAVIS, J. Nerv. & Ment. Dis. **70**:264 (Sept.) 1929.

This report is based on a study of forty-five patients made at Cornell Neurological Clinic. Forty-one, showing paroxysmal disorders, were given gastro-intestinal roentgen examinations. In one patient there was a six hour stasis of the stomach as well as stasis of the duodenum. Duodenal disturbance was indicated in 31 per cent of the examinations and duodenal stasis in 29 per cent. The author found about 5 per cent of his cases with symptoms referable to the uncinate gyrus, such as olfactory and gustatory aura — an observation that agrees with that of most observers. In twenty-nine patients the sella turcica was normal in size, shape and position. In one case the cell was smaller and in three, larger than normal, but this offers no proof that the pituitary gland plays an unimportant rôle in epilepsy.

The basal metabolic rate was determined in forty patients. An increased rate was obtained in only nine instances, only two of these reading above — 10 per cent. On the other hand, there were twenty-eight minus readings, and of these, fourteen were below the — 10 regarded as the normal lower limit, suggesting that patients subject to convulsive seizures tend to have a basal metabolism lower than normal.

Treatment was partly dietary and partly medicinal. A low residue diet in which food was taken at short intervals and in small amounts with limitation of bulk and fluids was advised in view of the duodenal disturbances. The diet usually markedly reduces the attacks, but after a few months the results seemed less brilliant. The patients were warned against overeating. Treatment with drugs was largely confined to phenobarbital, which produced no skin rash in the cases studied. In addition, pituitary gland has been prescribed in cases with subnormal

metabolic rates, sometimes in capsular form with aloin and phenobarbital. Although there was no cure in any of the forty-five cases, there has been a reduction of seizures from 50 to 75 per cent, the longest free interval being twenty-four months. In only twelve cases was no improvement reported. Grand mal attacks were more readily brought under control than petit mal, the latter condition being apparently increased by phenobarbital.

HART, Greenwich, Conn.

DENGUE FEVER AND THE NERVOUS SYSTEM. GEORG PAMBOUKIS, Schweiz. Arch. f. Neurol. u. Psychiat. **26**:51, 1930.

Pamboukis relates his experiences, as well as those of others, with dengue fever, which in the summer of 1928 afflicted nearly 80 per cent of the entire population of Athens. Pathologically, hyperemia and edema of the brain, as well as degeneratian of the nerve cells, were observed while clinically the patients complained of headaches, disturbances of sleep and pains of varying character. The author especially emphasizes the bradycardia, profuse sweating, low blood pressure and vasodilatation, which he attributes to parasympathetic stimulation as well as to a direct effect on the blood vessels themselves. A physician who had long suffered with attacks of tachycardia, which invariably occurred during previous attacks of fever, had a slight bradycardia while ill with dengue fever and obtained benefit from epinephrine, although after recovery from the fever the drug was found to have an alarming effect. The blood pressure was markedly reduced in some cases of hypertension.

The leukopenia and subcutaneous hemorrhages seemed to indicate a toxic effect on mesodermal tissue. Patients suffering from hemorrhages in the brain and cord showed a tendency to unusually rapid recovery under the influence of the fever. In a case of dementia paralytica a hemiplegia that had existed for some time cleared up, although the mental status remained the same following the acute infection. The author gives other instances of the assumed effect of the dengue fever toxin on the absorption of exudates. One case of parkinsonism was temporarily and another permanently improved. In conclusion the author states that further experience alone will show whether or not dengue fever can be used as a therapeutic agent. At present it would seem to be indicated in diseases in which an action on "histologically altered foci" is desired or in which conditions of sympathetic stimulation such as vasoconstriction exist.

DANIELS, Rochester, Minn.

AN OPERATION FOR THE CURE OF TIC DOULOUREUX. WALTER E. DANDY, Arch. Surg. **18**:687 (Feb.) 1929.

After reviewing the history of the treatment of trigeminal neuralgia, Dandy presents a new operation using a cerebellar approach. This method has been carried out on almost a hundred patients; the results were very satisfactory. An incision is made in the back of the neck and a small opening in the occipital bone. The cisterna magna is collapsed by puncture, and the cerebellar hemisphere elevated. The arachnoid over the tentorium is removed, and the sensory root of the fifth nerve is then observable. The nerve is severed in part or whole as it lies on the pons. Dandy believes that this is easier than the ordinary temporal route; he considers it a bloodless method. He also points out that keratitis is due to ganglion trauma; in the method described this trauma is absent. From experimental and clinical work Dandy concluded that pain fibers travel exclusively in the posterior part of the cross-section of the sensory root; by limiting incision to that area, the patient retains full motor function as well as normal touch sensation. Another advantage of the method is that the geniculate ganglion is safe, and postoperative facial palsy is rendered unlikely. The fact that the cerebellar approach would disclose an angle tumor if that were the cause of the tic is mentioned as a factor in favor of this operation. Dandy has used the

method since 1927 in all cases of trigeminal neuralgia; he believes that it combines surgical safety with therapeutic efficiency. The paper is illustrated with eighteen diagrams and pictures illustrating the steps of the operation.

DAVIDSON, Newark, N. J.

ANATOMIC STUDY OF THE BRAIN OF AN EXECUTED CRIMINAL. B. HECHST, Arch. f. Psychiat. **89**:131, 1929.

The author reports an anatomic investigation of the brain of a man, aged 34, who was executed after having killed his wife and three children. Clinical study of this person had brought out a series of symptoms that pointed to the probability that he was schizophrenic. The histologic observations follow: developmental anomalies in the structure of the cerebral hemispheres (in the sulcus simialis, the sulcus lunatus, the aster sulcorum parietalium Retzius and partial operculization of the occipital lobe); Cajal-Retzius cells, atypical cells in the marginal layer; abnormally large and irregularly shaped cells in the cerebral cortex; anomalies in the size, shape, position and structure of the Purkinje cells with swelling of the dendrites and axons of these cells. In the third and fifth layers of the cerebral cortex, he found diffuse as well as focal destruction of the cells which gave the impression of gaps in the layers. These were especially marked in the frontal and temporal lobes. They were not particularly related to the vascular supply and there were no signs of neuroglial reaction. The nerve cells, furthermore, showed signs of degenerative disease, sclerosis, vacuolization and lipoid degeneration. There were no signs that pointed to the presence of inflammatory disease or of mesodermal reaction. This process was restricted to the end-brain and was bilaterally symmetrical. There was no disease of the stem of the brain. The author is of the opinion that this form of pathology is frequently encountered in schizophrenia.

MALAMUD, Iowa City.

THE VALUE OF RADIOLOGIC EXAMINATION FOR THE DIAGNOSIS OF TUMORS SITUATED AT THE BASE OF THE SKULL. VIGGO CHRISTIANSEN, Acta psychiat. et neurol. **4**:301, 1929.

The author presents numerous cases as the basis for his conclusions that radiologic observations in tumors of the base of the skull are inferior to ophthalmic and neurologic studies as diagnostic measures of the presence, location or type of tumor. He points out that radiologists are unfamiliar with the appearance of the normal sella turcica and, particularly, have not studied intensively the alterations produced in the base of the skull by meningitis and other disease processes of infancy. He points out that a normal radiologic appearance does not exclude the presence of a tumor, while positive observations do not indicate precisely whether the change in contour is due to destruction by the tumor itself or by increased intracranial pressure resulting from a tumor situated in another region. In his experience, tumors situated above the tentorium more frequently show positive radiologic observations than subtentorial tumors.

Radiologic studies give no evidence as to the size of the tumor. There may be little change with large tumors and much destruction with small ones. In some cases, radiologic studies showed extensive destruction of the walls of the sella turcica, while at autopsy the sella was normal. He concludes that the diagnosis of a tumor at the base of the brain should depend more on the concomitance of ophthalmologic, neurologic and radiologic examinations than on the results of the last mentioned method of study alone.

PEARSON, Philadelphia.

THE PHYSICAL NATURE OF NERVOUS ACTION. RALPH S. LILLIE, Am. J. Psychiat. **9**:461 (Nov.) 1929.

The activity of the nervous system depends on transmission of impulses. This is a surface phenomenon electrically regulated. The stimulus may produce only an initial local disturbance, but there will be no functioning until it is propagated.

As the impulse travels, the nerve becomes temporarily negative at the point over which the impulse is passing. The part of the fiber which it has just left then becomes, for a brief instant, refractory. This process uses oxygen, elaborates carbon dioxide, and produces heat. Since the stimulus makes the nerve electrically negative, a miniature galvanic cell is set up with the tissue in advance being positive and the stimulated area negative. As a result, the current travels ahead and the next area becomes electrically negative. In this way the stimulus is propagated. By way of comparison, Little has devised the iron wire nerve. This consists of an iron wire suspended in nitric acid; a coat is formed which electrolytic reduction sets up by the metal-acid chain, and then by electrolytic oxidation is dissolved again. In this way an impulse, for instance a blow, can be transmitted along the wire as a series of chemical reactions. In several other ways this iron wire system shows a striking analogy to nerve tissue. Lillie offers his paper as a contribution to better harmony between clinical neurology and biologic physics.

DAVIDSON, Newark, N. J.

THE BI-COLORED GUAIAC TEST. EUGENE DE THURZO, Brain **52**:196 (June) 1929.

The colloidal gold test of Lange gives a "limit value" of 0.018 per cent; therefore, a normal spinal fluid may be within such bounds as to give a positive reaction. Not only is it essential in colloidal reactions to work out the salt and colloid sensitivity, but it is also necessary to examine separately the sensitiveness of each protein fraction: euglobulin, fibrin-globulin, pseudoglobulin and albumin. In the evaluation of disease the euglobulin fraction has the highest pathognomonic value. A relative increase usually indicates syphilitic involvement of the central nervous system.

The bicolored guaiac resin reaction seems to be an indicative test of the colloidal system of the spinal fluid, as it reacts with special sensitiveness toward euglobulin and pseudoglobulin, while it is little influenced by the other proteins. The test proves to have great sensitiveness in neurosyphilis. There is a parallelism between its reaction and the Wassermann reaction. In cases with high protein content of the spinal fluid, as in spinal compression, either negative or minimal responses were obtained. The greater sensitiveness of this test for euglobulin and pseudoglobulin, as compared to other colloidal reactions, evidences itself by deviation principally in the left zone.

The test is simple. The material is easy to prepare, and the color variation, which is definite, extends between red and vivid green.

BECK, Buffalo.

HEADACHES FROM CEREBRAL TUMORS: TREATMENT BY THE DIFFERENT FORMS OF DECOMPRESSIVE CRANIECTOMIES. RISER and R. SOREL, Rev. d'oto-neuro-opht. **7**:603 (Oct.) 1929.

In cerebral tumors, decompression is indicated as soon as signs of hypertension (especially papillary stasis) appear. The immediate effects are good, but in a large proportion of the cases the hypertension soon recurs. The most important reason for this is the presence of a progressive ventricular dilatation from blocking the cerebrospinal flow. If this blocking is not present or is transient, lateral decompression is efficacious.

In tumors of the posterior fossa, even Cushing's wide bilateral decompression affords only temporary relief. Suboccipital decompression is more efficacious when done early, especially in juxto-bulbopontile, cerebellar and subthalamic tumors. It is important to recognize the blockage of the ventricles. In case the lateral ventricles are blocked, the ventricular fluid is poor in albumin while the spinal fluid is much richer—from 0.1 to 0.2 Gm. and from 0.5 to 1 Gm., respectively. The injection of 3 mg. of phenolsulphonphthalein in a ventricle and the study of the rate of its elimination time in the spinal fluid or in the urine are valuable tests for blockage. Encephalography also gives important information. These

three observations—difference in albumin content, diminished rate of elimination of coloring matter and encephalography—demand suboccipital decompression, which must be wide and involve, in some cases, the posterior arc of the first vertebra.

DENNIS, Colorado Springs, Colo.

PITUITARY GLAND AND SUPRARENAL CORTEX. R. C. MOEHLIG, Arch. Int. Med. **44**:339 (Sept.) 1929.

Deploring the confusion existing among endocrinologists in regard to interglandular relationships, Moehlig offers to clarify the relationship between two of them—the pituitary and the suprarenal cortex—by citing instances of concomitant disturbance. He points out that anencephalic monsters usually are devoid of hypophyses or show serious defects in this gland, and that the same monsters also show defects in the cortical structure of the suprarenals. He cites experimental and clinical evidence to demonstrate that hypoplasia of one accompanies hypoplasia of the other, and similarly for hyperplasia. He implies the inevitableness of this occurrence, and explains it on the basis of embryo-hormonic connections which he mentions by reference rather than by description. He also refers to cholesterol metabolism as being affected by suprarenal or pituitary disorders, but assigns study of this problem to the future. Except for a single reference to his article in the same journal a year previously, he makes no reference to any experimental or clinical work of his own, basing his conclusions, rather, on a search of the literature.

DAVIDSON, Newark, N. J.

A CLINICAL STUDY OF AN HEREDO-FAMILIAL DISEASE RESEMBLING DISSEMINATED SCLEROSIS. FERGUS R. FERGUSON and MACDONALD CRITCHLEY, Brain **52**:203 (July) 1929.

A heredofamilial disease is described in which members of two generations of a family were affected. There are at least thirteen known members of the family who have had the disease. Any system in the brain or spinal cord may be involved: pyramidal, extrapyramidal, sensory or cerebellar. The degree to which these systems were involved, however, was so variable and the resulting clinical aspect so different, that the disease in individual members of the family resembled such widely divergent diseases as paralysis agitans and disseminated sclerosis.

The report is of unusual value because of the large number of cases. They illustrate how in such an affected family different clinical manifestations resembling almost all of the known types of heredofamilial ataxia can occur. The variation in the involvement of the different systems is relative, however, as each system was affected to some degree in all patients. Although similar cases were diagnosed as disseminated sclerosis, one in 1895, by Sir William Gowers, the authors do not attempt to classify the cases because of a lack of sufficient pathologic evidence. They prefer to leave this question open and to consider the diseases in this family, with the other examples of heredofamilial ataxias, as evidences of abiotrophies differing from each other merely in anatomic incidence or in viability.

BECK, Buffalo.

HEADACHES OF THE ADOLESCENT. J.-A. BARRÉ, Rev. d'oto-neuro-opht. **7**:609 (Oct.) 1929.

Naturally, headaches of recognized origin may occur during adolescence, but some are peculiar to this period of life. Headaches from intestinal worms, which did not reveal their etiology by the usual signs, were promptly cured after discovery of the eggs in the stools and the application of the appropriate treatment.

Two students observed that, on the slightest mental application, headaches were caused that lasted several days. Various measures to discover their source and bring relief were fruitless. The father confessed to an attack of syphilis pre-

viously, and although examination of the spinal fluids revealed no modification, antisyphilitic treatment was rapidly curative.

Almost always headaches due to a constant cause, but occurring only from time to time, are set loose by a secondary cause. Thus headaches from visual disturbance often appear only after chilling of the frontotemporal region; some syphilitic headaches occur only after overwork, and endocrine disturbances may give rise to headache only after an excess of masturbation. It is important not to permit the secondary causes to play the primary rôle in the etiology, and while therapy directed to them may at times show brilliant results they are only temporary until the primary cause is found and combated.

DENNIS, Colorado Springs, Colo.

FRACTURES OF THE TRANSVERSE PROCESSES OF THE LUMBAR VERTEBRAE. PAUL A. QUAINTANCE, Arch. Surg. **19**:968 (Dec.) 1929.

Quaintance confirms the by no means unanimous belief that a fracture of the transverse process of a vertebra may be due indirectly to action of the muscle. He presents a series of thirty-three patients with fractures of the transverse processes of the lumbar vertebrae, in four of whom the fracture was bilateral; he insists that if the spinous process was intact, both transverse processes could not have been fractured except by psoas or quadratus contraction. In addition to the general symptoms of injury of the back—weakness, stiffness and backache—fracture of a lumbar vertebra is diagnosed by tenderness localized immediately over the injured process, and by roentgen study. Prognosis in uncomplicated fractures is good, bony union always occurring except when there is wide separation of the fragments. The average period of disability was ten weeks, but some patients were disabled for seven months. Psychic factors unquestionably influence the period of disability. Treatment consists in physiologic rest by partial immobilization. Plaster jackets and other methods of absolute immobilization are, Quaintance believes, contraindicated. The commonest accidents causing this sort of fracture are blows, crushing injuries and falling from heights. The most frequent attitude at the time of injury was one of flexion. The third and fourth were the most susceptible of the lumbar vertebrae, and the first and fifth the most protected. Careful and complete roentgenographic study is urged in all cases of injury of the back.

THE RELATION OF ENDOCRINOPATHIC STATES TO CONDUCT DISORDERS OF CHILDREN. LOUIS A. LURIE, Am. J. Psychiat. **9**:285 (Sept.) 1929.

In a series of children wth behavior problems, Lurie found that endocrinopathic states made up over 16 per cent of the endogenous factors. Disturbance of the function of ductless gland manifested itself not only by direct effect, as for instance the hyperactivity of the sufferer from exophthalmic goiter or the intellectual retardation of the cretin, but also by indirect influence, as the attitude taken by a patient toward society and himself when he was conscious of such abnormalities as sexual infantilism or statuesque gigantism. For this reason Lurie believes that a careful estimate of endocrine balance is an essential part of the examination of every child presenting a behavior problem. The paper concludes with the presentation of the cases of five children whose disciplinary difficulties were due to ductless gland disturbance, two of them presenting Froehlich's syndrome and one dwarfism, the other two being irregularities of sexual development. In discussing this subject, Osnato suggested that some of the disturbances were traceable to incidental factors, as for instance the internal hydrocephalus associated with pituitary tumors, and Meyer warned against the danger of increasing the morbid outlook of these patients by emphasizing the endocrine abnormality.

A Study of the Functional Psychoses in Childhood. J. Kasanin and M. R. Kaufman, Am. J. Psychiat. **9**:307 (Sept.) 1929.

In the hope that the relatively less complicated personalities of childhood would permit of greater ease in the study of dynamic psychology, Kasanin and Kaufman conducted a survey of children under the age of 16 who were admitted to the Boston Psychopathic Hospital. Psychoses in childhood are rare, and of the 160 children admitted to that hospital in three years, only sixty-five had functional psychoses. Of this group schizophrenia, so diagnosed, constituted the major portion; after reclassification, however, it was thought that many of the cases of dementia praecox could be better placed elsewhere—as reactive, traumatic or toxic psychoses, some hysterical reactions, and a few undifferentiated conditions. The children suffering from dementia praecox showed alcoholism, insanity or delinquency in their heredity in almost every case. The problems of sexual adjustment seemed to play an important part in the mechanism of the psychoses, and sexual concern constituted a large part of the psychotic trend of the children. The precipitating factors were, in many cases, environmental difficulties of considerable seriousness.

Clinical Value of Kahn Test with Spinal Fluids. K. M. Davenport, Am. J. Syph. **13**:570 (Oct.) 1929.

After studying almost 500 cases of neurosyphilis and comparing the Kahn tests with the clinical observations, Davenport concludes that the positive result (in spinal fluid) is inevitably indicative of cerebrospinal syphilis. He points out, however, that the Kahn test gives frequent false negatives, so that a negative Kahn is not an indication of absence of cerebrospinal syphilis. He believes that in hospital practice the standard Kahn test should be used together with the presumptive test. This latter test he discusses in another article (*Am. J. Syph.* **13**:575 [Oct.] 1929). By the presumptive test is meant the one performed with the sensitized serum. This test, it is said, does not give false negatives. On the contrary, it frequently gives positive results when there is no clinical evidence of neurosyphilis. Davenport considers the possibility that a positive presumptive Kahn in the absence of clinical symptoms is indicative of a latent or very early neurosyphilis. In any case, he believes that the conservative but valuable standard Kahn test, combined with the very sensitive presumptive tests constitutes an important and useful diagnostic weapon.

Meningo-Encephalitis Due to Torula Histolytica. Willard J. Stone and B. F. Sturdivant, Arch. Int. Med. **44**:560 (Oct.) 1929.

After reviewing the eighteen cases of meningo-encephalitis due to *Torula histolytica,* the authors add a nineteenth to the literature. Like all of the others which involved the central nervous system, this case ended fatally. The patient first had headache and dimness of vision, and rigidity of the neck and fever developed only toward the end of his illness. Diagnosis was made in the early stages of the disease by the finding of fungi in the spinal fluid; however, as no adequate treatment was known, the patient died. Autopsy showed a generalized meningitis with the yeastlike torulae in the membranes, and an abscess in the cortex (temporal lobe) which was loaded with the fungi. The focus of the infection was found in the right lung, although no pulmonary symptoms had occurred. The authors believe that the condition is more common than its scanty references in the literature would suggest, and think that many cases of meningitis supposed to be tuberculous are really due to the torula.

Davidson, Newark, N. J.

HEADACHES IN UNILATERAL AMETROPIA. JEAN-SÉDAN, Rev. d'oto-neuro-opht. **7**:611 (Oct.) 1929.

It is understood that unilateral ametropia means normal vision in one eye and abnormal in the other, but with both eyes working together without amblyopia. Those who are blind in one eye and certain artisans, like watchmakers and jewel setters who use only one eye, are eliminated from consideration, for in these persons, headache is not produced by the ametropia. It is difficult to set an exact limit, but it seems that if there is a difference of more than from 2 to 3 diopters in the two eyes, headache is not apt to be produced.

The case of a roentgenologist, who suffered from headaches when he worked for long periods in the dark room, and who consulted the oculist for relief from blepharitis of the right eye, is reported. Examination revealed normal vision in the left eye and a pure hypermetropia in the right. Proper correction of the error in the right eye gave prompt relief to the headaches and caused rapid amelioration of the blepharitis. Two similar cases are cited.

DENNIS, Colorado Springs, Colo.

THE MENTAL FACTORS IN CRIME. WILLIAM HEALY, Ment. Hyg. **12**:761 (Oct.) 1928.

The study of persons who have been involved in various forms of crime indicates that knowledge of the mental antecedents in each personality is of utmost importance in understanding the nature of criminality. Developmental factors include such complex environmental influences that it is necessary to utilize the most thorough investigative procedures in each case. A survey of criminal behavior should be conducted on the basis of precision and care that characterizes the methods that have made for progress in the scientific and business world. Practical research has demonstrated in America a lack of intelligent organization for the treatment of the offender, a lack of coordination and cooperation, failure to study outcomes under present methods prescribed by law with no appreciation of the different types of criminalistic motives and backgrounds, and lack of understanding of the deeper mental factors involved.

EISLER, Chicago.

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DEUTSCHE ZEITSCHRIFT FÜR NERVENHEILKUNDE **111**:1 (Dec.) 1929

DR. W. J. BERNIS, Rochester, N. Y., *Abstracter*

THE CEREBROSPINAL FLUID IN ACUTE INFECTIONS OF THE NERVOUS SYSTEM.

DR. HANS DEMME, Hamburg.

During the last few years, changes in the cerebrospinal fluid were carefully studied in cases of acute infections of the nervous system, such as neuritis, sciatica, herpes zoster, poliomyelitis, disseminated encephalomyelitis, etc. The fluid was examined in as early a stage as was possible. The cerebrospinal fluid of animals experimented on was also more carefully studied. In experimental animals, the study was limited mainly to a cell count as the quantity of fluid was small. In patients, however, the customary globulin tests (Nonne-Apelt, Pandy, Weichbrodt), the cell count and the colloidal tests were performed, and the globulin was determined quantitatively. The colloidal test was limited to the mastic reaction, using Kafka's method, and a quantitative estimation of the albumin was made according to the Kafka-Samson method: total albumin, globulin and albumin. The determination of the hydration coefficient gave uncertain results and was therefore discarded. A sugar determination was done in a large number of cases, but led to no practical results. In the experiments, cases were used only when the Wassermann reaction of the blood and of the spinal fluid was negative.

In the infections of the nervous system that Pette enumerated in his paper there are constant changes in the spinal fluid, especially in herpes zoster. In nearly every case of herpes zoster, independent of its localization, there is a pleocytosis, which sometimes exceeds 100.3. At the same time there is an early increase in the albumin with a corresponding absence of the mastic curve. The pleocytosis remains longest in zoster. It disappears gradually as the inflammatory manifestations recede, while the albumin remains increased for some time.

In the various types of neuritis and polyneuritis many investigators found an increase in albumin with an absence of pleocytosis. This led to the conclusion that in these diseases it is not the peripheral nerve that is involved, but the process extends higher up, at least on the root intradurally. Queckenstedt and Heinze saw in the increase of albumin with an absence of pleocytosis in cases of neuritis and polyneuritis a condition similar to the changes in compression of the cord. They considered that the changes are due, not to a true inflammation, but to a toxic circulatory disturbance accompanied by edema. On the other hand, F. K. Walter, on the basis of a careful study, saw in the increased albumin the result of a true inflammatory process. In the series reported by Demme (table 1), an exception was observed in a case of polyneuritis of unknown etiology on the tenth day after the onset of symptoms; the cell count was 33.3, total albumin 10, globulin 3.4, albumin 6.6 and albumin equation 0.5. The mastic curve was 11251011121212.

The results recorded support the assumption that in these diseases the process is not limited to the peripheral nerves but involves at least the intradural roots. It also seems that at the beginning of the disease there is more or less pleocytosis, of a fleeting nature, which disappears within a few days. In the few cases in which Walter found a pleocytosis in the fluid, the puncture was done in an early stage. In a case of acute facial paralysis, in which lumbar puncture was done

eight days after the onset of the paralysis, Demme found a cell count of 236.3, total albumin 2.3, globulin 0.8, albumin 1.5, albumin equation 0.5 and a mastic curve of 123411111.

Apparently, an inflammatory process is present in the root of the nerve, spreading to the nuclear area, which after some time passes over from the blood stream into the spinal fluid. In the pure toxic, that is degenerative, polyneuritis (alcohol, arsenic, etc.) conditions are different. Here the relations are normal, including the mastic curve. It is apparently a toxic degenerative process involving the peripheral nerves. This type is to be distinguished from those due to agents producing a more central inflammatory process, such as diphtheria toxin and others.

It is known that in poliomyelitis changes in the fluid appear regularly in the early stages; however, they are also fleeting. The pleocytosis in the early stages may be considerable.

Demme found a high cell count (680.3) in a case of acute Landry's paralysis which ended fatally forty hours after the onset of the condition. Histologic studies showed that the most severe parenchymatous changes occurred mainly in the gray matter of the cord, with meningeal infiltration. Demme reports three cases of poliomyelitis. Cases 1 and 2 were mild, and the clinical manifestations disappeared after a few days; case 3 had passed the acute stage when the patient first came under observation.

TABLE 1.—*Results Obtained by Demme in Cases of Neuritis and Polyneuritis*

Diagnosis	Cells	Total Albumin	Globulin	Albumin	Albumin Equation	Duration of Disease
Normal		1.0	0.27	0.8	0.2-0.4	
Root neuritis.....	4.3	2.6	0.5	2.1	0.2	6 months
Polyneuritis	5.3	4.6	0.7	3.9	0.2	4 weeks
Lumbar neuritis.....	8.3	4.3	1.2	2.1	0.6	3 months
Sciatica	5.3	1.4	0.2	1.2	0.2	7 months
Sciatica	12.3	1.2	0.3	0.9	0.3	3 years
Perineal paresis.....	9.3	2.7	0.6	2.1	0.3	2 weeks
Polyneuritis	10.3	2.5	0.3	2.2	0.1	4 days
Polyneuritis	4.3	3.0	0.8	2.2	0.4	6 months
Sciatica	0	2.6	0.3	2.3	0.1	3 months

Demme has done much experimental work with poliomyelitis in monkeys. They were inoculated with poliomyelitis virus in various ways. The animals were first subjected to one or more lumbar punctures, and only those with a normal fluid were used for experimental purposes. There was an increase in the cell count a few days before the appearance of clinical manifestations. The virus employed by Demme was of high virulence and usually killed the animal in a few days. The cell count often reached several thousand. Soon after the appearance of the pleocytosis, the mastic curve regularly showed a small dip which increased in size from day to day. Demme also observed first a pleocytosis and later the appearance of pathologic albumins. The disappearance of the changes in the fluid could not be followed up since the animals soon died.

Examination of patients with late poliomyelitis show that the globulin may remain increased for a considerable time after the increased cell count has disappeared. It is then that the globulin gradually returns to normal.

Demme reports observations on the fluid in three cases of acute encephalomyelitis during the first stages. Case 1 was in a youth, aged 17, who became acutely ill with spinal and pontile symptoms and died of respiratory paralysis in eight days. Case 2 was in a man, aged 23, whose illness began with acute spinal disturbances, nystagmus and loss of abdominal reflexes. In a few weeks the symptoms disappeared, leaving slightly weak abdominal reflexes. Case 3 was in a man, aged 26, who became acutely ill with high fever, headaches and meningeal involvement. In a few days, a nuclear facial paralysis appeared with homolateral abducens and oculomotor disturbances. The patient died of respiratory paralysis

in six days. Postmortem examination showed a small hyperemic lesion in the right facial nuclear area which reached down to the pons. Histologically, inflammatory lesions were found around the blood vessels in the white substance.

In two cases of postvaccinal encephalitis, Demme found the spinal fluid entirely normal. This agrees with the observations by the largest number of investigators in similar cases, although some (Schürmann and others) reported a high pleocytosis and a positive globulin reaction. In encephalitis following measles, the reports are the same. Lust described changes in the spinal fluid (a mild pleocytosis and an increase in globulin) in some cases, while in others the fluids were normal. The changes in the fluid in acute encephalomyelitis are similar to those in multiple sclerosis. The changes in rabies and Borna's disease are not sufficiently known to warrant a definite conclusion.

Demme's conclusions, therefore, are that in herpes zoster, polyneuritis, sciatica and other types of neuritis changes are found in the spinal fluid which point to an inflammatory genesis in these diseases. In the acute stage there is an increase in the albumin in addition to a pleocytosis. This permits the assumption that the meninges partake in the disease.

TABLE 2.—*Results in Cases of Poliomyelitis*

Case	Cells	Total Albumin	Globulin	Albumin	Albumin Equation	Duration of Disease
1.....	50.3	1.8	0.2	1.6	0.1	5 days
2.....	25.3	1.0	0.2	0.8	0.25	5 days
3.....	20.3	2.3	1.3	1.3	0.8	6 days
Mastic curve						
Case 1: 1113531111						
Case 2: 3754321111						
Case 3: 235 7.5 7.8 53211						

TABLE 3.—*Results in Cases of Acute Encephalomyelitis*

Case	Cells	Total Albumin	Globulin	Albumin	Albumin Equation	Duration of Disease
1.....	364.3	3.3	1.2	2.1	0.6	4 days
2.....	35.3	1.8	0.8	1.0	0.8	2 weeks
3.....	240.3	2.1	0.4	1.7	0.2	3 days
	764.3	2.8	0.8	2.0	0.4	6 days

Experimentally, the pleocytosis in poliomyelitis precedes the changes in the mastic curve by two or three days. The observations in experiments on animals agree with those in human pathology. The pleocytosis precedes the onset of paralysis.

In acute encephalomyelitis the increase in the cell count may also appear in the early stage. The albumin quotient is on the average higher; the globulin is relatively higher than the albumin.

Important progress in knowledge of the changes in the cerebrospinal fluid that tend to clarify pathologic changes in the diseases considered is to be expected only when a deeper insight is gained into the kind and sources of the fluid, especially of the albumin bodies.

DISCUSSION

DR. WALTER, Bremen: I agree with Dr. Demme that in acute polyneuritis an inflammatory process is present. Apparently there is a higher permeability and the increased albumin in the fluid may be considered as hematogenous. In the later stages, pleocytosis is absent as is increased permeability, though an increase in the albumin still remains. Therefore I can no longer consider the latter as hematogenous. I believe that two explanations are possible: an increased flow in the perivascular spaces or a decrease in the escaping flow from the perineural lymph spaces.

THE EXTENSION OF THE ENCEPHALITIC REACTION IN BORNA'S DISEASE OF THE HORSE AND ITS RELATION TO ENCEPHALITIS EPIDEMICA, HEINE-MEDIN DISEASE AND HUMAN RABIES. DR. O. SEIFRIED, Giessen, and DR. H. SPATZ, Munich.

A full abstract of this article appears in the ARCH. NEUROL. & PSYCHIAT. **24**:1036 (Nov.) 1930.

DISCUSSION

DR. VON ECONOMO, Vienna, Austria: Grip is most likely caused by an ultravisible agent; nevertheless, grip encephalitis (to be distinguished from epidemic encephalitis and the diseases related to it) is characterized by mesodermal vascular inflammatory processes.

DR. PETTE, Magdeburg: The interpretation by Spatz of the histologic and biologic facts is in agreement with my ideas that poliomyelitis, epidemic encephalitis and Borna's disease are nosologically closely related. When I included herpes encephalitis in this group, I was led to it in the first place by biologic facts. The histologic picture in herpes encephalitis may vary considerably. I agree that in herpes encephalitis there is often a tendency to marked necrosis and to a diffuse extension of the process within the white matter. However, by employing less virulent strains the process is limited mainly to the gray matter. In such cases the process has considerable similarity to those of the aforementioned diseases.

DR. SPIELMEYER, Munich: Dr. Spatz has found an anatomic and etiologic relationship between the four polioencephalitis types of diseases that he has mentioned. But with herpes, which Dr. Pette puts in the very center of the classification, it does not agree. The histologic picture in herpes is anatomically entirely different from that in the other four diseases.

DR. GARTNER, Halle: There is a certain parallelism in the localization in the cases mentioned by Dr. Spatz and the storing of trypan blue as it comes from the blood stream. When trypan blue is injected intravenously, the glia limiting membrane, an important factor in the blood-cerebrospinal fluid boundary, keeps the dye away from the ectodermal part of the brain. An exception is observed in the hypophysial area where several nuclei (nucleus supra-opticus and tuber cinereum) store up the dye. May not, therefore, the hypophysial area be a locus minoris resistentiae and form the portal of entry, not only for the dissolved trypan blue, but also for ultrafiltrable viruses coming from the blood stream into the liquor system, and may not the localization of certain forms of encephalitis also be explained according to this principle?

DR. JAHNEL, Munich: Since Borna's disease can artificially be transmitted to other animals and to the monkey, it does not exclude the possibility of its being pathologic also to man. Perhaps such diseases until now have been diagnosed under other standards. Was it not observed that in people who were in contact with horses affected with Borna's disease suspected cerebral diseases did not develop?

DR. BENDA, Berlin: In this connection, I may report a case of chorea encephalitis in a youth, aged 17, who for a week showed marked hyperkinesis and herpes labialis; a rabbit which was inoculated showed a typical picture of encephalitis.

DR. SPATZ: It is hardly possible to assume that the stalk of the hypophysis is the entry point of infection.

THE PROBLEM OF THE PERSISTENCE OF THE INCITER IN THE CENTRAL NERVOUS SYSTEM. DR. G. STEINER, Heidelberg.

From the papers read here and the discussions that followed them, the conclusion must be reached that a one-sided division of the infectious diseases of the central nervous system based on biologic and morphologic aspects is as yet premature. Before such a scheme can be advanced it is important to dispose of a number of problems. One question concerns the length of time during which the inciter of infection remains in the central nervous system. Why does it persist?

Is a brief persistence sufficient for the inciter to bring about histologic changes? Is persistence possible without damage to the tissues? Many more questions may be added. First, however, one must be clear as to what are the possibilities of maintaining the persistence in the central nervous system. The following may be mentioned: 1. The inciter remaining constantly outside the central nervous system; toxins alone entering the central nervous system (tetanus). 2. The entrance of the inciter into the central nervous system and its immediate disappearance — no persistence — with: (*a*) disappearance of the original disease manifestations; (*b*) continuation of the disease with progression of the changes in the tissues (parkinsonism, especially nigral degeneration in epidemic encephalitis). 3. Entrance of the microbes into the central nervous system with direct apathogenic and inactive persistence, that is, without the development of an infectious disease *(Spirochaeta pallida* in the brain of the mouse; herpes virus in man). 4. Development of an infectious disease with ultimate persistence of the inciter only in the central nervous system. Indirect, inactive persistence following a general pathogenesis (spirochetal persistence in the central nervous system during the immune period in relapsing fever in man, the rat and the mouse). 5. Development of an infectious disease with the entrance of the inciter into the central nervous system; persistence of this disease and continuation, partly in periodic courses, of the living activity of the disease germ (propagation); active persistence with the subvariety of a change into temporary inactivity—intermittent active persistence (secondary syphilitic paralysis).

In all cases of infectious diseases of the central nervous system it is generally to be decided whether a persistent inciter is present and what its type is. Then the question will arise as to how this persistent inciter comes into being.

It might be assumed that histologic studies would be of assistance, that a particular definite histologic characteristic would indicate the presence of the inciter in each case. Dr. Pette assumed the plasma cells to be an indication of the presence of an active virus in the central nervous system. It is most unlikely that he still holds this opinion. Plasma cells are also found in a large variety of noninfectious diseases of the central nervous system. From studies in dementia paralytica it is known that spirochetes are present in places where there are no plasma cells, and again there are plasma cell infiltrations where no spirochetes are found. Hence the presence of plasma cells is no indication of the presence of an active virus.

Perhaps anatomic studies may be of aid. Dr. Spatz reported several types, each with its inflammatory area. It could be argued that the peculiarity of the distribution of the inflammatory predilections corresponds to the peculiarity of the entrance and persistence of the inciter in the central nervous system. Specimens from six cases of multiple sclerosis (illustrated by lantern slides) nearly all showed that the lateral area of the lateral ventricles is the site of predilection for demyelinization (corresponding somewhat to the stratum subcallosum) and is often symmetrical, and that in this area lies a kind of weather-vane for multiple sclerosis. The demyelinization often proceeds from the ventricle. Then there is usually an extension of the demyelinization perpendicular to the tangent of the ventricular curve, where it tends to flatten out parallel to the ventricular surface, or in a wedge-shaped formation with the ependyma as the base, with cones embedded into the healthy tissue. Lesions in the cortex, however, are not lacking; they are often found in the depth of a sulcus and at times also on the top of a gyrus, proceeding perpendicularly to the tangent of the convexity. If conclusions are to be drawn from this — under the supposition that multiple sclerosis is an infectious disease and that an inciter is present and persists in every lesion — it would lead to a deceptive conclusion. (That multiple sclerosis is an infectious disease must be accepted, according to Steiner, but he is not convinced by Pette's arguments concerning the importance of allergy in the development of multiple sclerosis.)

Steiner demonstrated preparations of rabbits inoculated subcutaneously with herpes encephalitis as another example from which one could argue as to the importance of histologic studies in clarifying the problems of persistence of an

inciter. The histologic changes are peculiar; inflammatory manifestations, in the sense of infiltration of the vascular wall, are rare; there are rather marked degenerative processes with a peculiar granular cell type of glial proliferation corresponding to the glia polyblasts of Spielmeyer. The histologic process in experimental herpes encephalitis is peculiar and is to be distinguished from the types of encephalitis which Pette has declared are anatomically and biologically related. The peculiar pseudolaminar softening of the cortical area in the more subacute or chronic herpes infections in the rabbit is lacking; this, however, represents an entirely characteristic distinguishing mark from all other forms of encephalitis. It concerns the peculiar histopathologic reactions of subacute and chronic cases of experimental herpes encephalitis. When one attempts to utilize the observations in multiple sclerosis and experimental herpes encephalitis in the problem of persistence of an inciter, one meets with disappointment. (The persistence of an inciter need not bring about anatomic changes; when it does so, the inciters may have disappeared before the anatomic process came to a standstill. In the histologic picture there is observed only a momentary snapshot of a long developed process in the diseased tissue as a reaction to the inciter and the opposite reactions of the inciter against the defensive substance of the host body. It may be that the tissue reactions, in the sense of observable histologic changes, are at no time dependent on the inciter itself. It can be assumed that the substances formed by the inciters, purely humoral, bring about pathologic tissue changes in places where the inciter never existed.)

It is established that after the expiration of the infection of the blood in the rat, the spirochetes causing recurrent fever are finally present only in the central nervous system of the immunized animal, and do not cause any anatomic changes. Here, then, there is the phenomenon of an inactive, indirect inciter persistence. How does it come about? Two theories might explain it: the neurotropic theory and "Barrientheorie." The first theory assumes that in the course of the infection there develops an affinity of the inciter for the central nervous substance; the second presupposes somewhere, the exact place being so far unknown, a barrier between the blood stream and the parenchyma of the central nervous system—a kind of a dividing wall which, although it permits the entrance of the inciter from the blood stream into the parenchyma, bars the body-formed defensive substance which destroys the spirochetes. Thus it could bring about merely a persistence of the inciter in the central nervous system.

The neurotropic theory can be discarded as the result of a simple experiment, in addition to other reasons; when a rat, immunized to recurrent fever, is united with a healthy rat by parabiosis, the persistent inciter present in the brain of the immune rat, possessing an active neurotropism, should also appear in the brain, especially in the central nervous system, of the healthy rat. But this is not the case even when with the parabiotic pair is united a third, likewise healthy, rat or an immune rat which has a reservoir of spirochetes in its brain. As for the "Barrientheorie," an experiment was made in which spirochetes were inoculated into the brain of a rat immune to recurrent fever. After the animal was killed and the brain was further inoculated there was observed a greater accumulation of spirochetes in the brain than in a control immune rat; according to the "Barrientheorie," the accumulation takes place as a result of the inciter remaining on the parenchymal side of the barrier. However, this experiment is not conclusive, since it depends merely on a comparison of the degree of infective processes between an immune rat inoculated with recurrent fever spirochetes and an immune rat not cerebrally inoculated.

In another experiment, an immune serum that was known to kill the spirochetes of recurrent fever was introduced into the brain of an immune rat. No destruction of the persistent spirochetes was observed. This, too, may be explained by the "Barrientheorie," since the substance injected into the brain does not reach the spirochetes; it remains on the side of the blood stream or in the vascular walls and does not reach the parenchymal side; hence it does not come in contact at all with the inciter of the disease.

Another experiment is striking. A mixture of immune serum (which was known to kill the spirochetes) and spirochetes was inoculated into healthy animals, into the brain of one animal and into other organs or into the blood stream of the other animals. The expectations were that no infection would develop. This was found to be true in the animals given injections in other organs or in the blood stream, but not in the animal receiving an inoculation into the brain; in the latter there developed a general infectious process. The Barrien theory fails to explain this, since this experiment had for its basis a healthy animal in which no immune substances had been found and in which the barrier, even if it were present, could not yet be effective. The experiment speaks rather for a kind of ability on the part of the brain or the central nervous tissue to make the immune substance harmless to the spirochetes, to absorb or neutralize it, a manifestation observed in such substances as diphtheria and tetanus toxins.

The neutralization of the immune bodies of recurrent fever by substances of the central nervous system has been proved to take place in vitro, where the effect of the immune bodies can be strengthened or weakened by the addition of brain substance. Therefore the central nervous tissues possess certain neutralization properties against the immune bodies of recurrent fever; this also explains why the inciter may persist in the central nervous system.

Cannot a somewhat similar analogy be assumed in the question of syphilis and metasyphilis? In syphilis there is an active persistence of the inciter in the central nervous system, even though there are inactive periods. Such an inactive period is observed between the secondary stage in syphilis and the appearance of dementia paralytica. It is assumed that the organisms remain latent in the central nervous system and that at the time when dementia paralytica sets in there is an enormous proliferation of the spirochetes. It must also be assumed that in syphilis there is a certain antagonism between the skin and the brain; the skin is the carrier of the strongest immune substance, while the brain, perhaps as a result of neutralization of immune substances, should be designated as immune-weak. Although the immune substance in syphilis is not known, facts accumulate that point to the formation of an immune substance in syphilis.

One can therefore distinguish three phases in the genesis and cure of metasyphilis. The first phase, in which there is sufficient immune substance free in the brain to exert a certain damaging influence on the inciter, and although it permits the existence of the early penetrating inciter it completely inhibits its growth. A second phase consists of the neutralization of all immune substances. There would then be a proliferation of the inciter and the beginning of dementia paralytica. (By the neutralization of the different immune substances and its failure, the author has in mind some such procedure as follows: After a repeated inflow of immune substances into the brain from the extracerebral storehouses, such as from the skin, the inflow fails to take place in the course of time and the absence of additional immune substances in the brain permits those that remain to be completely bound and neutralized. This is observed in other infectious diseases; the quantity of immune substances gradually diminishes and permits a second similar infection to develop. Georgi's newer experiments suggest that the spirochetes in the brains of persons with dementia paralytica during the latent period gradually adjust themselves to the immune substances of the brain; therefore, regardless of the fact that unbound immune bodies are still present, the spirochetes regain the ability to multiply.) Finally, the third phase would condition the necessary therapeutic overflow of immune substances into the central nervous system, transporting them from the skin and bringing them into the brain, thus destroying the inciter and bringing about a cure in dementia paralytica. The overflow of the immune substances must be such that the central nervous tissues are not in a position to neutralize the overflow and its effect on the spirochetes.

In this way it is possible to explain how acute infectious diseases may cure dementia paralytica. The artificially induced infection brings about an increased transportation of immune substances from the skin, thus making possible a

specific opposite reaction by means of a nonspecific infection therapy. It also explains how in some cases of arsphenamine dermatitis, when a breaking up of skin tissues might set free immune substances from the skin, an improvement in dementia paralytica may take place.

It may be pointed out that this conception offers an explanation for the peculiar manifestations now frequently observed as a result of infection therapy, namely, the appearance of tertiary syphilitic—gummatous—processes in the skin after treatment with malaria and recurrent fever, even some time after the infection therapy. A diminution of the immune substances in the skin might rekindle the syphilitic process in the skin by the persistent latent germs.

DISCUSSION

Dr. Jahnel, Munich: Chicken spirochetes belong to the inciters that, although they enter the central nervous system, do not persist there. In birds the spirochetes disappear first from the blood, then from the internal organs and last from the central nervous system. Also in mammals when the transmission of a large dose brought about an unusual infection, the chicken spirochetes showed the same relation. Other spirochetes, such as the inciters of syphilis, show a different relationship; in the mouse they are regularly present in the brain; in the rabbit, only exceptionally.

Dr. A. Jakob, Hamburg: Multiple sclerosis may occur in a symmetrical form, but does not do so necessarily. In one case of multiple sclerosis Steiner's argentophil products were found without having a definitely spirochetal character.

Dr. F. Plaut, Munich: The term "neurotropism" should be employed only with reference to those inciters of disease which primarily affect the nervous system, chiefly or exclusively, or which are capable of maintaining themselves in the nervous system after the termination of a general infection. Work with syphilis or with spirochetes of recurrent fever shows that there is no general neurotropism; this neurotropism can be spoken of only as a virus in relation to one or another species of animals. The stock of the same virus varies greatly in its neurotropic ability, and a neurotropic stock may lose its tendency to affect the nervous system without any known cause. With special care it is sometimes possible to make some stocks neurotropic. Syphilitic spirochetes can be made neurotropic for the rabbit when they are first passed through the brain of the mouse (Schlossberger). Not all the spirochetes of syphilis are rendered neurotropic for the rabbit by first being passed through the brain of the mouse. The spirochetes of recurrent fever remain longer in the brain of the rat than in the brain of the mouse. By repeated passage through the brain of the rat, the duration persistence for the brain of the mouse can be increased, and this remains through further passages in the brain of the mouse. Passage through the brain of the rabbit prolongs the persistence of the recurrent fever spirochetes in the brain of the mouse, but they lose their property with the next passage through the brain of the mouse.

Pathophysiology of the Production of Sleep with Special Reference to Visual Motility. Dr. F. G. von Stockert, Halle.

In the spring, a number of cases of abortive types of encephalitis were observed in which narcoleptic manifestations were present. (This is only a preliminary report.) For several months the patients manifested psychic changes. They were easily excitable, complained of severe headaches and had a great tendency to go to sleep; nearly all of them suffered from occasional diplopia. The cardinal symptoms in epidemic encephalitis are disturbances of the ocular muscles and a tendency to sleep. Pötzl called attention to the relation between the condition of the eyes and sleep. In the cases observed by von Stockert this relationship was evident. Attacks of loss of consciousness with catalepsy, up to deep sleep, could be brought on with each turning of the eyes, and the more extreme, quicker and

longer the fixation the more definite were the manifestations. It was especially remarkable that in fixation on a fixed object, first a convergent cramp appeared, which expressed itself in double vision, and then sleep set in. This was shown spontaneously when the patients were reading; first the letters appeared double and then the patients went to sleep.

(Velhagen, in a separate paper, reported these cases from the ophthalmologic point of view. His observations were essentially negative.—*Abstracter.)*

Another point of interest is that merely closing the eyes would also bring on unconsciousness and sleep. It must be assumed here that the upward rolling of the eyeballs, Bell's phenomenon, and not the lack of visual impressions was responsible for the appearance of a state of sleep, since the same patient remained entirely awake in a dark room; only a few minutes after he closed his eyes in the dark room he went to sleep. It is to be recalled that Pötzl and Trömner assumed a causal relation between Bell's phenomenon and sleep.

In other cases of postencephalitis Stockert observed that sleep could be brought on by means of visual attempts. In a patient with acute encephalitis, with marked hyperkinesis, spontaneous sleep was brought on by visual fixation. She could be awakened by shaking and calling. Of special interest is the parkinsonian case demonstrated by Bostroem; in addition to rigor, this patient showed marked catalepsy during an attack of visual fixation.

Von Stockert observed that all his patients reacted to hyperventilation and inhalation of amyl nitrite; that a short time afterward they first showed a fixed stare or a definite convergent cramp and then passed into a state of sleep from which they were awakened with greater difficulty than from the sleep coming on after visual attempts. Two patients fell asleep a few minutes after entering a warm bath.

Von Stockert is inclined to believe that the improved circulation in the brain, caused by the three conditions mentioned, is responsible for the activation of the sensitized sleep center. In hyperventilation the venous sinuses are sucked out as a result of the negative pressure in the thorax and hence an inflow of more arterial blood is permitted; with inhalation of amyl nitrite there develops a dilatation of the cerebral blood vessels, while at the same time the minute volume of the blood from the heart is increased; a warm bath permits the assumption that the same conditions are produced.

Hans Strauss was able to bring on a state of sleep in a case of parkinsonism by ventilation. Foerster described the appearance of cataleptic manifestations in an epileptic patient after ventilation. When it is considered that a condition of tetany can be brought on by ventilation, which according to Kraus and Zondek is considered a special form of vagotonia, another interpretation may be offered for the onset of the sleep thus produced. Heilig and Hoff, in 1925, pointed out the parasympathetic evidence in physiologic sleep. W. R. Hess and Mingazzini, on such considerations, have built up their theory of vegetative sleep.

The study of the calcium content in sleep induced by the inhalation of amyl nitrite gave further support to this assumption. There was an increase of calcium in the serum up to 25 per cent. Thus a definite vagotonic condition of the organism can be assumed. The calcium change was found in every case, and also in healthy subjects after the inhalation of amyl nitrite. Von Stockert does not think that the increase of calcium in the blood alone is to be held responsible for bringing on sleep. He gave a patient intravenous injections of calcium (calcium chloride urea), which brought on sensations of heat, bitter taste, etc., but could not bring on sleep.

Concerning the provocation of sleep in convergence cramp, the experiences gained by hyperventilation in tetany and especially Foerster's observation in epilepsy are of interest. In encephalitic cases, the nuclear area of the ocular muscles is to be considered as the cramp center and the cramp of the ocular muscles as similar to other manifestations of cramp. Georgi assumed a similar point of view.

DISCUSSION

DR. TRÖMNER, Hamburg: Dr. von Stockert's observations are interesting, if hysteria and training can be excluded. Also, during the normal approach of sleep (hypnagogic phase) dissociated ocular attitudes appear, which is a partial manifestation of the entire sleep complex. Was there not present in the cases described a loss of the "affective tonus?"

DR. VON ECONOMO: Dr. von Stockert's cases are excellent examples of the abnormal reaction of the sleep-regulating center in persons who have sustained encephalitic injury.

DR. LAMPL, Prague, Czechoslovakia: The histories in these cases give little or no indication for the assumption of an encephalitis; in addition, these patients, aside from the symptoms described, show no indication of involvement of the basal ganglia, especially no parkinsonism; again, they remind one of hysteria. In a similar case, a patient who passed through a long period of an undetermined fever showed no signs of parkinsonism. He complained only of paroxysmal attacks of convergent cramps, when he saw double and enlarged pictures; this passed over into a state of sleep, with the making of stepping movements at the same time. In this case there was a vestibular disturbance, a vertical nystagmus and, during the attack, an alternating anisocoria. The attacks began to come on more often and a functional disturbance was suspected, but from a number of observations it appears that the diagnosis of encephalitis was justified.

DR. VON STOCKERT: Two cases showed a distinct loss of tonus. The falling of the patient is not always in the direction of the visual fixation, although in many cases it is, and agrees with Goldstein's theory.

CONTRASTING ACTIVITY IN THE INNERVATION OF LIFE. DR. L. R. MÜLLER, Erlangen.

The automatic activity of the heart is slowed by vagus stimuli and is accelerated by the sympathetic, especially the nervi accelerantes. In the stomach, conditions are entirely different; the motor and secretory activity comes from the vagus while it is inhibited by the sympathetic. For other internal organs which are not directly supplied by the vagus, such double and contrasting activity cannot be easily proved anatomically and experimentally. Therefore it was formerly assumed that the activity of most of the internal organs is influenced entirely by fiber plexuses from the sympathetic ganglia. It was also assumed that the blood vessels are innervated by vasoconstrictors, and that a dilatation of the vessels depends on the relieving of the tonus by the constrictors. This conception was disproved by the observation that stimulating the lingual nerve that goes to the chorda tympani produces dilatation of the blood vessels of the salivary gland, and that excitation of the nervus erigens running from the lower sacral plexus to the genitals causes an active hyperemia of the sexual organs. It was then admitted that the sympathetic is concerned not only in the innervation of the heart and stomach, but also as an opposing partner for some other organs. Since the cells of origin of the chorda tympani, as well as those of the vagus, are to be sought in the medulla, and since the nervus erigens takes origin from the lower sacral cord, this group was spoken of as a "bulbar and sacral antonomic system" and this parasympathetic system was added to the sympathetic ganglionated cord.

Further studies have shown that visceral antagonistic innervation is not limited to the heart, stomach, pupil and blood vessels of the corpora cavernosa, but that it extends to all internal organs. Striking proof, such as is obtained by stimulation of the vagus and the sympathetic to the heart or stomach, is not so easily demonstrated in other organs because the parasympathetic tracts are nowhere so isolated and so easily found as in the vagus and more often run together in the same nerve trunk with the sympathetic. Now, however, it must be assumed that not only is the activity of the heart and the stomach regulated

by a double antagonistic nervous supply, but all other organs are likewise regulated. For the innervation of the pupil, the salivary gland, the intestines, the bladder and the sexual organs, this antagonism can be demonstrated by animal experimentation. On the other hand, such conclusive evidence has not yet appeared as regards the skin, blood vessels of the skin, sweat glands, sebaceous glands and pilomotors. When the caliber of the blood vessels of the salivary glands and of the sexual organs is regulated by vasoconstrictors and vasodilators, it is to be assumed that the blood vessels of the skin are also innervated, not only by constrictors but also by dilators.

Foerster, in 1928, stated that he was able to demonstrate in man vasodilatory manifestations of the skin, with definite metameric boundaries from all posterior roots. At that time, L. R. Müller expressed the opinion that sweat secretion is influenced not only by the sympathetic but also by the parasympathetic system. This was substantiated by L. Guttmann. If all blood vessels and sweat glands of the face, trunk and extremities are supplied not only by the sympathetic but also by the parasympathetic system, then the innervation centers of the parasympathetic system cannot, as has been assumed until now, be limited to small areas, such as the medulla for the vagus and the chorda tympani, and the conus terminalis for the nervus erigens. It must rather extend along the entire cervical, dorsal and lumbar cord. The transitional area between the anterior and posterior horn, the "substantia intermedia," is to be considered the seat of the parasympathetic centers.

While the sympathetic tracts, the ganglion cells of which are to be sought on the top and lateral border of the lateral horn, leave the cord through the anterior roots, it seems that the vasodilators and other parasympathetic fibers pass through the posterior roots. Ken Kuré and his co-workers observed in the posterior roots a considerable number of fine medullary sheaths which do not degenerate after sectioning of the spinal ganglion. Kuré suspected that the cells of origin were located in the gray substance between the anterior and posterior horns.

Cajal has found in the posterior root efferent fibers which split up around multipolar ganglion cells of the spinal ganglion.

Dieden has shown, in experiments on cats, that there are tracts in the posterior root which inhibit the secretion of sweat in the paw.

The finer regulation of the internal organs, the harmonious cooperation, that is necessary for the proper maintenance of life can be brought about only through stimulation and inhibition. The play of organ innervation on the superficial blood vessels of the hair can be observed through the microscope, and the activity of the sweat glands in the psychogalvanic reflex through the galvanoscope. Stimulation alone could not bring about such fine regulation as is necessary for the assurance of a uniform body temperature.

The sympathetic and parasympathetic superordinated centers in the medulla, in the mibrain and in the interbrain are in need of antagonistic workings, that is, of stimulatory and inhibitory tracts, in order to harmonize the functions of the individual systems, such as the blood stream, digestion and excretion. Through the sleep-regulating center in the posterior part of the interbrain, exhaustion leads to sleep and to an overbalance of the tonus in the parasympathetic system. Contraction of the pupils, slowing of the heart's activity, breathing, the lowering of blood pressure and of the bodily temperature and the lively activity of the stomach and intestines are due to diminished tonus of the sympathetic and increased tonus of the parasympathetic. The daily experience that bodily rest alone is not sufficient, that only sleep brings refreshment and recovery, that sleep takes place in infants and convalescents without bodily fatigue being present, and that growth and regaining of strength demand sleep justify the assumption that recovery and replacement of fatigued cells are produced by an increase in parasympathetic tonus by the sleep-regulating center which brings on a dilatation of the blood vessels. Cannon expressed the same opinion. He assigned to the parasympathetic system the stimulation for assimilation, for "anabolism." Cannon considered the sympathetic as the nerve of "dissimilation," of "catabolism," because under the

influence of the sympathetic there is an increase in metabolism. The activity of the heart becomes more lively, respiration quickens, and the increase in the blood sugar and the increase in the output of epinephrine in the blood increase the functional ability of the striated musculature and hence cause an increase in metabolism.

An increase in parasympathetic innervation leads to pleasurable sensations, to the assertion of life. The appetite and desire for food are due to stimulation of the vagus and the contraction of the empty stomach. Sexual desire is due also to a stimulation of the nervus erigens coming from the parasympathetic sacral autonomic system.

On the other hand, all unpleasant sensations come with an increase in the sympathetic tonus. During fear, the stimulation of the sympathetic vasoconstrictors drives the blood out of the blood vessels. The face turns pale. In rage, as Cannon has shown, there is an increased output of epinephrine in the blood and thereby an increase of sympathetic tonus, exophthalmos, and an increased activity of the striated muscles. Worry, through lessening of the appetite and increase in catabolism, brings on a loss of weight. Fear of danger brings on, through the sympathetic system, a cold sweat, a pallor of the face and erection of the hair. A depressed state of mind does not permit the rise of the sexual impulse. A strong unpleasant experience or an intense bodily pain, though stimulation of the sympathetic, will bring about dilatation of the pupils, pallor of the face, increased flow of the saliva, activity of the heart and a standstill of the gastro-intestinal movements.

There is a contrary activity, not only between the sympathetic and the parasympathetic innervation, but also between the nervous system which regulates the expressions of life of the internal organs and those parts of the nervous system through which impressions are received from the outer world and by means of which it reacts on the outer world. While the vegetative system is engaged with digestion, dislike for work forces one to take bodily and mental rest. A similar condition is present when the outer temperature is high. The innervation of life is similar to the activity in the cosmos, day and night, summer and winter, and periods of tropical growth. It is a constant change and a contrary activity.

The greatest and last contrary activity, as regards the innervation of life activity, is its cessation, the physiologic old age—death. The individual being is only a rapid, passing manifestation on the endless road of the different forms of life. In man the activity curve reaches its highest point around the thirties. The life stream that flows decreases in the aged, and one has only to await the time when the lowering line of one's energy and hence life's innervation reach faster or slower the zero point.

DISCUSSION

Dr. O. Foerster, Breslau: Sweat's inhibitory influence by stimulating the posterior roots was recently shown by Schilf to be present in lower animals. There is a great difference in the extensity of the effect of the stimulus from stimulating the anterior or the posterior roots. A single anterior thoracolumbar root contains preganglion sweat secretion fibers for a number of skin dermatomes; therefore, from stimulating them there appear definite sweat secretions in all those dermatomes. But the posterior root contains sweat inhibitory fibers for its appertained dermatome alone. When the anterior and posterior thoracic roots are stimulated at the same time, there remains in the midst of the large number of sweating dermatomes, a single dermatome corresponding to the stimulated posterior root which is free from sweating.

Dr. Marburg, Vienna: Spiegel's work shows that the ascending systems are in the anterolateral tracts attached to the pain and temperature paths, and that the descending tracts are found near the pyramidal tracts.

Changes in the Central Nervous System in Yellow Fever. Dr. A. Jakob, Hamburg, Dr. Amadeo Fialho and Dr. E. L. Villela, Rio de Janeiro, Brazil.

In 1928, while Jakob was on a visit to Rio de Janeiro, yellow fever was prevalent. This gave the authors an opportunity to study the pathologic anatomy of the central nervous system in this disease. So far, investigations on this subject

have been meager. The patients often show symptoms of markedly anxious delusions, which become more severe in fatal cases toward the end of the disease. Fourteen cases were studied by the authors.

The changes in other parts of the body are characterized mainly, as Rocha-Lima described in 1913, by a severe fatty degeneration of the liver, with dispersed necrosis at the intermediary border zone, by severe parenchymatous degeneration of the kidneys, with lime casts and hemorrhages, and by erythrophagocytosis in the spleen.

The macroscopic appearances of the central nervous system are usually normal. Microscopic studies show definite changes in all cases.

The leptomeninges show in some places a mild small cell infiltration with a few lymphocytes and macrophages. Sometimes there are blood pigments in the macrophages. More seldom, at the base of the brain or on the convexity, there is similar and somewhat more marked infiltration, with edematous swelling of the pial meshes.

The gray matter of the central nervous system, especially the cortex and the striatum, shows marked fatty degeneration of the ganglion cells, particularly the larger elements, and of the cells of the vessel walls (endothelial and adventitial cells). The fatty degeneration of the ganglion cells goes together with a glial proliferation of the Hortega and microglia elements, which often assumes the character of a lesion. Fine fatty droplets are found in both glia elements, especially in the macroglia.

The lymph sheaths of the blood vessels in the gray and also in the white substance are at times stuffed with macrophages, which occasionally contain iron pigments. Here and there are also found more marked lymphocytic infiltrations. Around the blood vessels there are, less frequently, edematous areas of the tissue surrounded by a glia cell reaction.

Ammon's horn shows marked fatty degeneration of the ganglion cells. This is present in the fascia dentata as well as in its pyramidal area, especially in Sommer's area.

In Nissl preparations, the ganglion cells are in a condition of fine webby degeneration with chromatolysis and more or less nuclear degeneration. The proliferation of the glia also appears to be definite. In the cortex, mainly in laminae III and V, there are areas of obliteration, at times of a definite perivascular type, and in lamina I there is an active glial reaction. In a few places in the cortex there is diffuse ganglion cell degeneration and loss of cortical tissue, especially in lamina III. Also the pyramidal band in Ammon's horn shows areas of obliteration accompanied by reactive glia manifestations. Similar changes are observed in the striatum and in the cerebellum where, in a few places, there can definitely be observed an acute destruction of the Purkinje cells, caused by glia shrublike formations in the cerebellar molecular zone.

In four cases there were small perivascular granular formations. In the neighborhood of blood vessels mildly infiltrated with lymphocytes there were areas showing proliferated Hortega and macroglia cells, occasionally mixed with lymphocytes. In the neighborhood of these lesions there were often diffuse macroglial proliferations. The granulomas in the four cases were found in the gray nuclei of the medulla and pons.

In six cases there were marked degenerations; at times, lesions in the cerebellar cortex. In one there was a loss of Purkinje cells, a marked diffuse shrublike formation in the molecular zone and considerable proliferation of Bergmann's glia cells in the Purkinje layer.

The cases showed in addition a perivascular lumen in the granular layer with the capillaries showing marked degenerative changes.

Finally, in one case there was found a marked lesion of acute degeneration of the granular and Purkinje layers with considerable loss of granular and Purkinje cells.

In three cases the dentatum showed severe fatty degeneration of the ganglion cells, with marked glia proliferation.

In two cases the parenchymatous degeneration of the striatum was extraordinary. The ganglion cells were degenerated to an unusual degree; the macroglia were more markedly proliferated and in the pallidum, near the ganglion cell degeneration, there were found in the glia cells pigments, some containing iron.

The changes found in this disease are similar to those in other toxic and severe infectious diseases—in typhoid and especially in typhus—with the differences that in yellow fever there is a high grade fatty degeneration of the ganglion cells and more fatty degeneration of the vessel wall elements; also, the striatum and cerebellum seem regularly to be involved in yellow fever.

LATE STAGE OF ENCEPHALITIS IN MEASLES: OBSERVATIONS ON THE HISTOLOGY AND PATHOGENESIS OF ENCEPHALITIS IN MEASLES. KARL M. WALTHARD, Zurich, Switzerland.

In a child, aged 3, a typical case of measles developed, with a temperature of 103 F. On the fifth day, the temperature came down to normal. On the next day the temperature was again from 103 to 104 F. She began to show athetotic and choreic movements in the right hand, had convulsions and became stuporous; the eyes turned upward, at times there was strabismus, and she kept turning the head in all directions. All reflexes except the abdominal ones were present; there was no Babinski sign; the pupillary reaction was absent; the corneal reflex was present. The pressure of the spinal fluid was increased, the Pandy test + +, 5.5 cells and leukocytes 14,000. After three weeks the condition became worse. Gradually rigidity of all extremities developed and she became unconscious; there was a positive Babinski sign and nystagmus was present. The patient died four and one-half weeks after the symptoms first set in.

The histologic observation can be summarized as: extensive glial proliferation around the blood vessels with marked destruction of the myelin sheaths and axis cylinders in the area of the centrum semiovale of both hemispheres and in the basal ganglia. Here and there were extensive diffuse glial proliferations in the cortex and in the anterior horn of the cord. There was mild perivascular round cell proliferation around some blood vessels.

The histologic observations differ essentially from those of the early stages of encephalitis in measles as described by Wohlwill and Redlich. In the early stage, there was described a glia cell syncytium around the venous blood vessels, forming a border around the vessel. In the syncytia there are seldom found mobile cells that serve for the removal of destroyed nerve substance; more often there are the cells designated by Spielmeyer as glial macrophages which can be compared with Maximow's mesenchymal polyblasts. In the late stage, however, there are found only wrecking and clearing glia cells in the form of fat granular cells. The original fine border in the Nissl picture becomes markedly enlarged, thickened and fused together, and may be mistaken for lesions. Also in the cortex the process is further advanced and the glial proliferation is more diffuse. The degree of the myelin sheath destruction corresponds to the quantity of the fat granular cells present. The axis cylinders are correspondingly destroyed, while in the early stage they are largely spared.

In contrast to the early stage there is lacking here a definite glial proliferation under the ependyma; furthermore, the glial border in the periphery of the cord, as described by Wohlwill, is lacking. On the other hand, the anterior horn substance of the cord is often affected.

The patients in the cases described by Wohlwill and others died within four or five days, while the patient of Walthard was under observation for four and one-half weeks; therefore, in contrast to the other cases, the author designates his case as a late stage.

According to the conception of the investigator, the process can be designated either as an inflammation or as degeneration. If the glial proliferation is considered as an inflammatory manifestation, then the process must be interpreted as inflammatory. If, however, inflammation is considered only as those processes in

which, in addition to the alterative and proliferative ectodermal components, there is also an exudative manifestation on the part of the mesoderm, the observations in the case here reported must be designated as degenerative. This question, however, is only secondary to the more important one, namely, that of etiology, for an infection caused by a living virus is capable of producing a pure degeneration as well as a pure inflammation, and on the other hand a noninfectious agent may produce a histologic picture of inflammation. The histologic observations in the case here reported do not necessarily point to an infection, perhaps even less than do those of early cases. The histologic observations are no indication of whether an infection was present or not.

This case is of interest in connection with the problem of the relationship of multiple sclerosis to the group of postinfectious encephalomyelitis. This case, presenting a typical late stage of encephalitis in measles, does not show distinct lesions such as occur in multiple sclerosis. It is true that occasionally there are observed lesion-like areas with sharp demarcations, especially in the basal ganglia, but most of the lesions are not sharply marked off from the normal tissue. They are not true lesions, but rather more or less thick zones of demyelinization. Another point of interest is that they show a complete destruction of the axis cylinders in the demyelinated areas. Contrary to the lesions in multiple sclerosis, the axis cylinders here are not spared; they disintegrate like the myelin sheath. When, in the early stage of this disease, the axis cylinder remains intact, it is to be explained by the fact that it is less vulnerable.

These two reasons argue against bringing multiple sclerosis in this group of diseases.

THERAPY FOR CHRONIC EPIDEMIC ENCEPHALITIS. DR. LAMPL, Prague, Czechoslovakia.

Lampl reports his treatment for chronic epidemic encephalitis by two methods, which according to his observations offer the best results. The first method is based on the principle of organotherapy. This method has not as yet passed the experimental stage, but has been fairly successful in the hands of the author. The second method is symptomatic.

Of late, considerable thought has been given to organotherapy in organic nervous diseases. Bier and Gehrke prepared a nerve substance which appears to have been of considerable benefit in a number of cases of tabes and multiple sclerosis. Soon after their publication, Haberlandt and Steinach reported on the effect of a brain hormone which should exert special influence on tonus. Whether it is a true hormone in the sense of Starling is questionable. However, Lampl, on the basis of his observations, is ready to substantiate that in the brain substance, especially in the extract, there appear to be present, under certain conditions, one or more bodies which specifically influence tonus. Lampl, at first in collaboration with Prof. Wilhelm Wiechowski and later with Drexler, has been engaged in these experiments for more than two years. In 1928, he reported that a number of patients with chronic encephalitis treated by this method improved or were entirely cured. The method consists in giving nerve substance in combination with injections of autoserum and albumin. He uses an extract from the medial thalamus, the corpus luysii and, under certain conditions, the substantia nigra. The extract is thermolabile and even the outer temperature at the time when the animal is killed is not without effect. A change of 4 degrees will affect the extract. (Lampl fails to give a more detailed description of how the extract is prepared.—*Abstracter.)*

In the symptomatic treatment for chronic encephalitis the best results so far have been secured with scopolamine hydrobromide and atropine. Lampl and Wiechowski found the extract of the crude drug much more effective than the chemically pure substance. But the extract must be standardized, otherwise its effectiveness varies. So far they have made two preparations that are biologically standardized and that exclude unpleasant associated manifestations. One, which

contains a titrated scopolia root extract, is given (from one to two tablets three times a day), followed by strong black coffee and plenty of fluids. After from three to six days, it is followed by injections of protein in slowly increasing doses to bring about fever. The production of fever is contraindicated in patients with diseases of internal organs, or soon after some infectious disease; likewise, special care is advisable in dispensary cases. The fever-producing treatment should not be given in full doses. The number of fever-producing injections varies between ten and fifteen; the intramuscular between twelve and twenty. The scopolia root extract is continued during the period of protein therapy, but later is reduced to one-half the quantity. After the protein therapy is finished, the second preparation is given. This is stated to contain various extracts of scopolia, carniolica, hyoscyamus niger, nicotiana rustica, atropa belladonna and datura stramonium. At the same time, calcium compounds are given intramuscularly once daily or once in two days, for from twenty to twenty-five injections.

One can support this therapy by diathermy of the head, applying the electrodes over the forehead and the back of the neck for about fifteen minutes.

NERVOUS DISTURBANCES IN PERNICIOUS ANEMIA AND LIVER THERAPY. DR. HANS CURSCHMANN, Rostock.

Observing the improvement obtained in pernicious anemia with liver therapy, the question naturally arises whether the nervous symptoms of this disease are likewise favorably influenced by this treatment. For years, Curschmann and his co-workers have paid special attention not alone to the neurologic and psychic symptoms of such patients; in addition, all etiologically unclear cases of spinal diseases have been investigated for a possible beginning or for a remission in the course of pernicious anemia. This experience, Curschmann believes, gave him actual figures for the frequency of spinal complications in pernicious anemia before and after the introduction of liver therapy. The results were: of over 230 cases of pernicious anemia up to the spring of 1926, about 90 per cent presented spinal symptoms in the form of paresthesias, hypesthesias, hyperesthesias, hyporeflexia and areflexia, the Babinski sign, more or less pseudotabes, or (somewhat oftener) a spastic syndrome.

Since the introduction of liver therapy, about one and three-quarters years ago, Curschmann has not observed an increase in the spinal symptoms above 90 per cent.

In over 300 cases of pernicious anemia Curschmann did not find definite and true cerebral or psychic symptoms.

In pernicious anemia does liver therapy influence the spinal symptoms favorably as it does the blood picture? Curschmann's answer to this question is in the negative. He has not observed a single case in which the spinal symptoms, especially the sensory, motor and reflex disturbances, were really improved by liver therapy. Curschmann reports two typical cases of pernicious anemia complicated by spinal disturbances in which liver therapy brought about a remission, but failed to affect the spinal symptoms, which progressed; he observed this in over a dozen other cases. Again, Curschmann observed severe cases of pernicious anemia in which no objective spinal symptoms were present until improvement set in. He reports a case of marked pernicious anemia in a woman, aged 47, who showed great improvement under liver therapy. It was then that the spinal symptoms began to increase. The gait became very ataxic, and paresthesia and hypesthesia increased; at the same time there appeared an increase in the patellar and achilles reflexes, foot clonus and double Babinski sign.

The failure of liver therapy to cause improvement in the symptoms of funicular myelitis not only is true in definite cases of pernicious anemia but also in cases in which the spinal cord syndrome is definite but the blood picture is still in the early stage and would be missed without special hematolgic examinations.

This relationship not only is of practical importance, but is theoretically interesting. The different therapeutic-prognostic relationship between the blood

picture and the spinal syndrome reaffirms the old teaching of Minnich that the anemia and the myelitis are the result of a common unknown noxa, which at times affects more the blood, at times more the spinal cord, or again may affect both at the same time. There are cases in which the spinal disease precedes the observable anemia for a long time, even for years. It contradicts Hennenberg's conception that the anemia leads to a nutritional disturbance of the cord, which brings about a lowered resistance against the noxa. Against Hennenberg's theory is also the fact that in other types in severe secondary anemias and in leukemias, there are seldom disturbances of the cord.

From the observations reported, it might be concluded that the liver cure, as Stepp has observed, has not the effect of a vitamin. The therapy represents symptomatic treatment for the damage to the blood, but not an etriotropic control of the causes of the combined symptoms.

From the observations it is apparent that, in addition to the improvement in the blood in pernicious anemia as a result of liver therapy, the funicular myelitis requires its own treatment. This is not an easy undertaking; arsenic and transfusions have proved failures. If fever therapy is instituted, it should be done after liver therapy has brought about a remission in the blood picture.

DISCUSSION

Dr. Redlich, Vienna, Austria: I have before called attention to the importance of investigating all unclear spinal cases for pernicious anemia. I have seen a large number of such cases. In one, there was atrophy of the tongue with fibrillary tremor, and in another there was atrophy of the quadriceps. This is important because Bielschowsky has found changes in the peripheral motor nerves in pernicious anemia. Unfortunately, my therapeutic experiences agree with those of Curschmann. Although there was considerable improvement in the blood, there was none or very little passive improvement in the nervous manifestations.

Dr. Lottig, Hamburg: Five cases reported from the Heidelberg clinic and three from Nonne's clinic have recently shown that objective improvements do take place in funicular spinal disease.

Dr. Trömner, Hamburg: Curschmann's (as well as Trömner's) conception that the spinal and blood diseases are only indirectly related diseases receives support from cases of spinal diseases in which the blood remains always normal. Three of the eight cases reported by Trömner six years ago were of this type. The question comes up whether it is not a systematic pathologic degeneration of the cord—for this speak the occasional pure lateral or posterior column diseases—or whether it is a neurotoxic effect—for this speak the occasional neuritic symptoms, such as pain, paresthesias in the fingers, pain on pressure and occasional muscular atrophy.

Dr. Runge, Chemnitz: In pernicious anemia with spinal symptoms, psychic disturbance occurs more often than is usually conceded. Lately I have seen three such cases. I observed no improvement with liver therapy.

Dr. von Witzleben, Dresden: Improvements occur not only in the subjective symptoms, but also in the objective neurologic symptoms.

Dr. Determann, Wiesbaden: If the loss of cholesterin is to be held responsible for the nervous system becoming affected in pernicious anemia, why is it that the cord is almost exclusively involved and not the brain and the peripheral nerves?

Dr. H. Curschmann: Hasty conclusions as regards improvement in the spinal symptoms in pernicious anemia after liver therapy should be avoided. I doubt whether they are of any duration; spontaneous remissions take place not only in the blood but also in the spinal symptoms. As to why the brain and peripheral nerves are not involved in pernicious anemia, the answer is that the noxa is selective for the cord, as the virus of syphilis is for the posterior columns, or as lead is for the extensors, etc.

DISTURBANCES OF THE CIRCULATION OF THE CEREBROSPINAL FLUID AND ITS RESORPTION IN PSYCHOSES. DR. L. GUTTMANN, Hamburg and Friedrichsberg.

Three additional methods are employed by Guttmann for the examination in psychic cases: encephalography, the cerebrospinal fluid resorption test of Foerster and the relation of the albumins in the fluid according to Kafka. Combination of these studies, especially in unclear psychoses, offers an insight into the pathophysiology of the central nervous system. Guttmann examined over ninety patients with schizophrenia and about forty encephalograms were made. In making the encephalograms Guttmann is attempting to answer two questions: 1. In cases of schizophrenia, which occasionally suggest clinically an organic process, is it possible to determine the organic nature and the extent? This question Guttmann answers in the affirmative; he reports two cases.

CASE 1.—A woman, aged 42, presented paranoic symptoms with acoustic and occasional optic hallucinations. She was at times excitable. Experimental psychologic examination showed disturbances of attention, comprehension and association. This led to a suspicion of organic brain disease. Neurologic examination gave negative results except for an increase in the deep reflexes. An encephalogram—the air-fluid exchange was from 190 to 200 cc.—showed a high grade of increase in the subarachnoid space of the convexity such as is observed in severe atrophy of the brain. Both anterior horns were markedly deformed and in an eccentric position; the third ventricle showed considerable enlargement. A lateral view showed considerable atrophy of the brain, especially in the parietal and frontal areas; it showed also hydrocephalus of the posterior horns.

CASE 2.—A woman, aged 50, who was paranoic, showed stereotypy, no spontaneity and no connection with her surroundings and was negativistic. The air-fluid exchange was from 180 to 190 cc. The encephalogram showed a moderate grade of communicating hydrocephalus which may be designated, according to the fluid resorption tests, as hydrocephalus hypersecretorious. The protein relation showed pathologic value, with special emphasis on the albumins.

2. In true schizophrenia does the roentgenogram of the brain guarantee an insight into the pathophysiologic process? Guttmann calls attention to the large quantities of spinal fluid which he often was able to withdraw in these cases; at times it was more than 200 or 250 cc. This in itself indicates pathologic changes. In some cases there was an increase in pressure. Encephalography was of no less interest in these cases.

In a schizophrenic patient, aged 40, who was also paranoic, hallucinated and stereotyped, there was atrophy of the cortex, especially in the frontal area. In another patient, aged 35, who was maniacal, a marked catatonic stupor developed and he had to be fed by tube; he showed an air-fluid exchange of from 250 to 260 cc.; the lateral encephalogram showed a definite increase in the surface shadow, likewise in the frontal area. The ventricles were not outlined. The anteroposterior view showed definite closure of the ventricles. The test for fluid resorption with sodium iodide, according to Foerster, showed in both cases, a delay both in the beginning and in the duration of elimination. Kafka's protein relation showed it to be pathologic in the individual components. It is to be noted that in some cases the removal of the fluid has a favorable influence; some patients showed temporary improvement.

Of special interest in the encephalographic studies in advanced cases of schizophrenia from the point of anatomic localization is the fact that the main changes in the subarachnoid space of the convexity are found in the frontal area of the brain. This agrees with anatomic experience in schizophrenia that the histopathology extends to the frontal part of the brain. The question still remains open whether the changes in the subarachanoid space in true schizophrenia, as observed in the encephalographic picture, are an expression of cortical atrophy in the affected areas of the brain or a primary disturbance of the fluid circulation. There are indications

that both factors are present. There is no parallelism between the individual clinical psychic symptoms and a special disease of particular areas of the brain. Especially is there no connection between acoustic and optic hallucinations and diseases of the temporal and occipital lobes.

As regards the disturbances of the resorption of cerebrospinal fluid in psychoses, Guttmann found, in thirty-six of fifty cases observed, more or less delayed onset in the secretion of iodine. In many cases the duration of secretion was delayed. Twenty-three showed a pathologic albumin relation. On the other hand, there were cases with a normal absorption of fluid and pathologic albumin relation and vice versa. These facts indicate that finer methods of examination may reveal organic disturbances in the cerebrospinal fluid system in schizophrenia; on the other hand, from a comparison of the disturbance in resorption with the albumin relation one learns how manifold the disturbances of the cerebrospinal fluid system may be in such cases. The fluid disturbances in circulation and resorption indicate the polymorphism of schizophrenia.

DISCUSSION

DR. WALTER, Bremen: The delay in bringing the substance into the cerebrospinal fluid may depend on a delay in the exchange of substances between the fluid and the blood, but this is not necessarily true. Much more so is it caused by retention in the rest of the body.

DR. O. FOERSTER, Breslau: Regarding Walter's statement, it can be said that a careful test of the activity of the kidneys is presupposed, especially with reference to the fact that intravenously injected sodium iodide is excreted in the urine; if iodine is injected into the cerebrospinal space and fails to appear in the urine renal function is important in determining whether it is due to a resorption deficiency. In many cases in which intraspinally injected iodine did not appear in the urine, by renewed tapping Foerster was able to show that the iodine remained in the cerebrospinal space. Again, Foerster was able to show that in many cases in which there was failure of the appearance of the iodine in the urine and the conclusion had been drawn that there was a lack of fluid resorption, on opening the cisterna cerebellomedullaris and permitting extensive drainage of the fluid into the musculature of the neck—a method which Foerster considered most useful in hydrocephalus aresorpticus—the iodine promptly appeared in the urine.

DR. WEYGANDT, Hamburg: In schizophrenia one is dealing with hereditarily conditioned endocrines, a disposition influencing the entire organism, which in some cases, from unknown causes, passes over into the disease. The encephalographic observations and the increase in albumin in the spinal fluid, as well as the changes in the sediment, are of the greatest importance.

DR. GUTTMANN: Functional renal tests are always made. As to where the blocking takes place, in some cases, I believe that the answer must be guarded. But the fact that after intraspinal and intraventricular injections of sodium iodine the iodine can be shown by lumbar puncture to be present for a long time, it can be concluded that, in these cases, at least, the obstruction is in the exchange relation between the cerebrospinal fluid and the blood. In other cases the obstruction may possibly be in other parts.

Book Reviews

REFLEX ACTION. A STUDY IN THE HISTORY OF PHYSIOLOGICAL PSYCHOLOGY. By FRANKLIN FEARING, M.D. Price, $6.50. Pp. 350. Baltimore: Williams & Wilkins Company, 1930.

This book is a most educational one for neurologists not versed in the history of medicine. It is valuable, however, not alone for historians, for by tracing the development of scientific thought concerning reflexes the reader gains a new idea of what a reflex really is. Reflexes are the elemental units in the mechanism of perpetual equilibration. Physiologists have studied and are studying at the present time these numerous machine-like, inevitable reactions of the organism — reflexes existing from the very birth of the animal, and due therefore to the inherent organization of the nervous system. Since the foundation of the nervous activities of both men and animals is made up of the "aggregate of reflexes," Pavlov believes that their study is of fundamental importance to physiology. The study of reflexes and instincts may be expected to lead eventually to a complete understanding of the total behavior of the organism.

The author's object is to tell the story of the development of the concept of reflex action and of the phenomena on which it is based. Such a study should throw light on the causes of the present lack of agreement as to the use of the term reflex. So far as possible, however, the object is to survey the investigations and theories of neuromuscular adjustment in chronologic order, with particular reference to the theories of reflex action.

The key to the book is given in a table of "The Chronology of Reflex Action." This consists of a list of names showing the dates of various contributors to the field, and their historical time relations. The list plots an interesting curve of the advance of neurology. The more important names are: Descartes 1596-1650, Glisson 1597-1677, Willis 1621-1675, Swammerdam 1637-1680, Duverny 1648-1730, Whytt 1714-1766, Prochaska 1749-1820, Bell 1774-1842, Hall 1790-1857, Müller 1801-1858, Lewes 1817-1878, Lotze 1817-1881, Eckhard 1822-1905, Pflüger 1829-1910, Wundt 1832-1920, Waldeyer 1836-1921, Pavlov 1849-, Sherrington 1857-, and Lucas 1879-1916.

The work of these men and of many others is presented and discussed; many well chosen quotations are inserted, and references are carefully noted. Thus the book is useful not only as a compendium of information regarding reflex action, but as a starting point in looking up references to the work of any man or school. The indexes and bibliography are exceptionally well done.

The author divides the historical development into five stages: (1) The prescientific periods (until the seventeenth century). These include everything until the time of Descartes in the seventeenth century. The work of the Greek and Roman physicians and philosophers, and the biologic speculations of the Middle Ages are of great interest and importance, but no attempt is made to examine them in the present volume. (2) The speculative period (1650-1750). This includes the era beginning with the description of a certain species of involuntary action by Descartes in the seventeenth century and ending with the publication in 1751 of Whytt's book on the involuntary motions of animals. Although the work of Willis, Duverny and others was to some extent empiric, the concept of the reflex arc did not possess a solid foundation in experimental observation until the period that was ushered in by the experiments of Whytt on the spinal cord. The work of Swammerdam in the latter part of the seventeenth century on the nerve-muscle response was in the nature of an exception to the foregoing characterization, but his work seems to have been neglected by the majority of his contemporaries. (3) The period of nascent experimentation (1750-1831). This period

extended from the time of Whytt until the work of Marshall Hall on the reflex functions of the spinal cord in 1832. It was characterized by a certain amount of crude experimentation. During this time, however, the word "reflex" came into general scientific use. (4) The period of increased knowledge of the structural components of the reflex arc (1832-1906). The work of Sir Charles Bell and Marshall Hall gave the concept of reflex action a fixed position in both physiology and medicine. This is the era of the simple mechanical reflex and includes the discovery of a vast number of separate reflex mechanisms as a result of new experimental technics. (5) The modern period. The publication in 1906 of Sherrington's work on the integrative action of the nervous system is a convenient date with which to mark the change from the hypothesis which regards the reflex as a simple stimulus-response sequence to that which considers it as an integrating unit in the adjustive activities of the organism.

Especially interesting are the contributions of the seventeenth century. These may be summarized as follows: (1) The theory of bodily automatism as stated by Descartes and elaborated by Willis. This theory involved the specific statement of the principle of reflex action, and included the description of numerous specific automatic acts which modern physiology would recognize as reflex. (2) The contributions of Swammerdam, especially in the use of the nerve-muscle preparation as a technic in the study of neuromuscular phenomena. (3) The contributions of Swammerdam, Borelli, Glisson, Stenson and Mayow which tended to show that the traditional concept of animal spirits was inadequate so far as neuromuscular processes were concerned. (4) The study of the effects on behavior of the experimental destruction of various segments of the central nervous system. The theories and contributions of Willis, Perrault, Duverny, Chirac, Preston, Mayow and others should be mentioned in this connection.

To the reader it may be surprising that "Monsieur Duverny, in the year 1673, . . . took the brain and cerebellum from a pigeon, and in place thereof, filled the cranium with flax, notwithstanding which it lived some time, searched for aliment, did the ordinary functions of life, and had the use of sense." Moreover, Willis had about this time distinguished between the seats of voluntary and involuntary motion, the cerebrum being the higher center, and the cerebellum the lower and more automatic center.

In the eighteenth century, Robert Whytt was the conspicuous contributor; he emphasized the necessity of the relationship between stimulus and response in the case of involuntary motion. He established the spinal cord as the structure which may independently preside over involuntary functions, and pointed out the protective function of involuntary motions.

The advances and controversies of the early nineteenth century are interestingly described. The latter part of this century brought with it the elaboration of technic, and the pertinent experiments became so diverse that the author describes modern work under subject headings. Thus there is a good chapter on "The Inhibition of Reflex Action." Another on "The Reflex Maintenance of Posture" describes especially the work of Sherrington and Liddell, which brings under a single explanatory principle phenomena that have hitherto appeared to be widely divergent. Posture, tonus and tendon phenomena have been the subjects of prolonged controversy. He adds that the intimate relationship between posture and tonus and the connection between the latter and the psychic process of attention seem to indicate the possibility of renewed attack on the problem of attention.

The chapter on "Motor Automatisms and Reflex Action" is less clear, perhaps necessarily so, for as the author points out lack of knowledge in this field illustrates that the classification of behavior in categories, the limits of which are rigidly fixed, together with the adoption of a specific terminology frequently serve to check scientific advance, unless the categories are regarded merely as temporary and convenient devices for purposes of scientific discussion. The terms "reflex," "involuntary," "voluntary" and "automatic" are more than classificatory designations; they have come to carry a burden of implications, philosophic, physiologic and psychologic, as to the nature of nervous function. It is essential that they

be used with caution, and that the hypothetic implications which they have acquired during the seventeenth and eighteenth centuries be regarded as provisional only.

The consideration of "Modern Concepts" is the last chapter. This also lacks the conciseness of the first part of the book, and the terminology of modern psychologists confuses the reader to some extent. The summary, however, somewhat clarifies the reader's mind and leaves a definite basis for discussion and choice of point of view. The examination of reflex theory as expressed in representative physiologic and psychologic texts and treatises resulted in a threefold classification which may be summarized as follows:

1. Reflex action under the first ("specific") concept is regarded as possessing certain physiologic and psychologic characteristics which distinguish it from all other kinds of action. There is disagreement as to the nature of these criteria, but a list made up from various sources is as follows: (1) the reflex is not conditioned by consciousness; (2) it is involuntary; (3) the time from the reception of the stimulus to the beginning of the response is short as compared with the "voluntary" or "willed" reactions; (4) neurologically, the reflex does not involve the cerebral cortex; (5) it is a type of behavior which is unlearned; i. e., it is based on inherited neural mechanisms, (6) it is predictable, uniform and definite, i. e., given a certain type of stimulus and a certain receptor organ, the response is relatively invariable; (7) reflex action serves some adjustive or protective purpose; (8) structurally, the reflex involves a receptor, afferent and efferent conduction in a synaptic nervous system, and an effector.

2. Reflex action under the second ("genetic") concept has certain definite characteristics in its simple form, but there is no sharp break in the series of responses in which the reflex or other primitive type of response represents one extreme and complex "volutional" responses, the other.

3. Reflex action under the third ("mechanical") concept is based on a fixed neural mechanism, including afferent and efferent conduction and receptor and effector organs; this neural arrangement is assumed to underlie and predetermine all behavior. The characteristics of the simple spinal reflex, e.g., invariability and innateness, are applied to all behavior. It is usually the functioning of the simple reflex arc that is described, and it is by implication that the characteristics of this functioning are carried over to all action. Under the "mechanical" theory, automatisms and "volition" are explained in terms of fixed mechanisms. Habits (automatisms) are merely certain reflex responses which have become attached to certain stimuli by a process of conditioning.

To these three is added the conception of the "Gestalt" school of psychology, which has reacted vigorously against mechanistic concepts. It is a fundamental tenet of this school that the properties of organic life are not adequately explained by special properties — either inherited or acquired — which enforce order. In particular they reject the concept, which is a fundamental postulate of mechanistic physiology, that inherited typographic arrangements compel the course of organic processes, for example, the nervous impulse, to follow a fixed and predetermined path. In place of the order imposed by inherited and acquired arrangements, a third type of functional interpretation is proposed which Köhler calls "dynamical self-distribution." According to this theory, there is a dynamic interaction within the system itself which is a fundamental factor in determining the distribution of forces. The organism is regarded as an adjusting, self-regulating apparatus in which order is enforced, not by preexisting neural arrangements, but by dynamic factors involved in constant interaction between the processes in the organism itself in relation to the environment.

Throughout the book the author avoids expressing his own opinion. He does choose his quotations, however, in a way that leads the reader to believe that he is antagonistic to the "behaviorists" and prefers to follow Holt and Köhler more than the purely mechanistic psychologists. In such a piece of work there must be omissions and choice. It is surprising, however, that no mention is made of the important experiments of Coghill and Detwiler. Altogether the book is

admirable, and with Sherrington's "Integrative Action of the Nervous System" and Fulton's "Muscular Contraction and the Reflex Control of Movement," one has a triad that gives the earnest student a remarkably complete exposition of reflex physiology.

INTRODUCTION BIOLOGIQUE À L'ÉTUDE DE LA NEUROLOGIE ET DE LA PSYCHOPATHOLOGIE. INTÉGRATION ET DESINTÉGRATION DE LA FONCTION. By C. VON MONAKOW and R. MOURGUE. Price, 80 francs. Pp. 416. Paris: Librairie Félix Alcan, 1928.

This is an extraordinary book—the climax and not the introduction of the life-work of a very personal individualist, a Slav aristocrat, who followed his father to Switzerland and made his career with a remarkably steadfast independence and purpose. He began as an experimental anatomist, following the Gudden principles and applying them to the pathologic anatomy of the human brain and the results of secondary degeneration, also in material obtained from Munk's laboratory dealing with experiments on localization in the dog, etc. Then came a phase of clinical expansion and the writing of the noteworthy large volume in Nothnagel's system; a growing interest in the functional aspects of neurology, and the building up of mature life out of primitive steps and sensorimotor assets; a strong tendency to trust this localization in time, i. e., the course of neural and functional evolution, more than the customary generalizations from anatomy, and a development much more akin to Hughlings Jackson's than to Wernicke's and other popular localizers' schemes. With his diaschisis concept (the suspension of function through the distance effect of degeneration processes), a disregard of detailed studies of fine localization in the cortex and an increasing attention to the broadest philosophic needs, one need not be surprised that during the war there occurred something like a conversion to the broadest possible problems and solutions, on the structural side, a surprising faith in the explanatory significance of the choroid plexus fluid and, on the functional side, a development of biologic concepts including psychology and neurology under a personal terminology that was broader and more human than the reflexologies of his St. Petersburg-Leningrad contemporaries but that was also unwilling to recognize the worth-whileness of a wholesome pluralism allowing reasonably detached spheres of competence to anatomy, physiology and psychology and sociology, or whatever subgroups of biology the nature of topics and of methods would suggest. Attempting to give a summary of the book would readily become a crime. It must be read, as it is written, in lucid French by the able co-worker Mourgue under von Monakow's guidance, and as it is rendered in German by von Monakow's assistant, Katzenstein in an excellent translation. This review is intended to give a glimpse into the perspectives of the work.

True to the best tradition of French authorship, the writers give a full summary of the disposition of the work in the preface and in an introductory chapter, which initiates the reader into the broad biologic conceptions with the help of a number of neologisms that should be used only with due respect for the total system: Integration of movement and chronogenic localization, and a characterization of biologic principles incorporating life, as von Monakow and Mourgue saw it, namely, self-regulation, latency and its soil, self-recreation, diaschisis and chronogenic localization, primordiality of instinct, and diaspasis or fragmentation.

The first half of the book deals with the integration, the differentiation of the world of instincts, the hormé operating under the principle of klisis (choice) and ekklisis (refusal) in a sphere of instincts (formative, preservative, sexual, social and religious) and a sphere of "orientation and causation." The instincts (hormeterias) blend in part with the second sphere acquired through experience and reason as noohormeterias, i. e., instinct influenced by reason, and include the biologic conscience, syneidesis or autoregulation of functions, including the compensatory processes in malformations and regenerations, and what is actually called "conscience" up to what is met in criminality, toxicomania and "arrivism" or bald

philosophy of success. The evolution of motility is the common basis of instinct and of what the authors discuss as "causality," which is further elaborated as the "sphere of orientation and causality," gnosis, protodiakrisis or primordial discrimination, inhibition or sympathetic or antipathetic anastole, orientation in time and praxia, the development of language and of causality in the sense of reason (infantile, fragmented, agglutinated, root-branch or critically objective and inductive). The second half of the book treats of disintegration (pages 165 to 392): (1) the morphologic disorders through breaks of continuity of the nervous substance, the disintegration of movements, apraxia, agnosia, aphasia and mental orientation (delusions, affections of the noohormeteria and compensatory functions of syneidesis, the biologic "conscience"); (2) the secretory disorders of the nervous system as seen in the problem of the psychoneuroses and psychoses, especially schizophrenia; there is an almost monographic chapter on von Monakow's very personal views of the ectodermic-mesodermic barrier and the secretory and distributory troubles concerning the cerebrospinal fluid.

This simple enumeration should make it clear that the chapters have to be read as wholes because of the need of all the concrete material subsumed under the new points of view. The reader will at once see that a large fund of knowledge of neural structure—comparative, embryologic and adult—and of experimental and pathologico-anatomic and functional data is incorporated and calls for a reintegration under exceedingly broad and, at the same time, penetrating principles. The term "introduction" is not to be taken in the sense of elementary discussion for the beginner (although undoubtedly it presents von Monakow's mode of instruction), but an introduction to the testament and envoi of a great worker and his co-worker. Detailed reviews have been published (Meyer, A.: *Nervenarzt*, 1929, vol. 8. Winkler: *Schweiz. Arch. f. Neurol. u. Psychiat.* **23**:329, 1928. Minkowski: *Zentralbl. f. d. ges. Neurol. u. Psychiat.*, vol. 57, p. 36). The present outline and characterization are offered to arouse the interest of the reader to turn to one of the two original versions, the French or the German. The successive chapters should be made the subject of "seminar" evenings; they are full of essential detail.

It is difficult to say to what extent the English-speaking neuropsychiatric world will fall in line with the ideology of this great Russian-Swiss and the Bergson pupil Mourgue. There is, on the one hand, a definite submersion of a dynamically conceived psychology or anthropology in von Monakow's neurobiology, with a frank inclusion even of the religious vision of man. Probably most neurologists would prefer the shaping of a well organized chapter on objective as well as subjective psychobiology and a chapter on neurology, anatomo-physiologic, but not pretending to make a psychobiologic presentation unnecessary or at least merely incidental to a neurologizing biology. The other provocative issue would be the rôle of the cerebrospinal fluid system as the supposed essence of the basic regulation of the neuropsychologic functioning of man. Does the fluid possess the differentiation and the means of distribution sufficient to carry the burden attributed to it? Moreover, has not von Monakow surrendered the morphologic work too hastily, including the correction of some of his own most cherished views? The evolution of the conceptions of the optic pathways, additions to the anatomy of the thalamus, a more intimate study of the differentiation of the cortex and a more critical and concrete analysis and synthesis of motility would have added much to a sense of security, very much needed if one is to be prepared for the infusion of a large dose of syneidesis and other very human conceptions into a neurobiologic view of man. The reviewer is nevertheless convinced that American neurologists will derive an unusual amount of stimulation and gratification from the perusal of this document of one of the greatest personalities in their field. It is a monument that will attract and inspire every wanderer in the most comprehensive and ultimately also the most vital domain linking the natural sciences and humanism.

PSYCHOANALYSIS OF TOTAL PERSONALITY. By FRANZ ALEXANDER, M.D. Translated by Bernard Glück and Bertrand D. Lewin, with a prefatory note by A. A. Brill. Price, $3.50. Pp. 176. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1930.

When Freud, in 1924, evolved his later formulation of the categories of the mind, the Id, the Ego and the Super-Ego, he gave to psychoanalytic theory a new impetus for discussion and speculation. Freud himself has referred to these formulations as mythical conceptions. Nevertheless, they have been fully and rather avidly adopted by practically all the adherents of his school, and are today forming the basis for a revision of old and the establishment of new valuations of mental dynamics and economics. To be sure the fundamentals of therapeutic psychoanalytic practice and aims have not been essentially altered by the new concepts of the Super-Ego and Id, nor even by the somewhat more radical postulates of a life and a death instinct. They have, however, tended to make more clear in the mind of the analyst the general psychologic interaction of antagonistic instinctive urges and repressing forces. Alexander refers to the "Psychoanalysis of Total Personality" as the "economic balance of the claims of instinct and the counter claims of reality operating as anxiety and morality" (page 68). These conflicting tendencies have always been taken into consideration in previous analyses, for in the psychoanalysis of a neurotic symptom its position and value in relation to the other psychologic reactions of the patient have always been thoroughly considered by the majority of psychoanalysts.

Alexander's book consists of a series of nine lectures given by him as a part of the course in psychoanalytic instruction offered by the Berlin Psychoanalytic Institute. In his foreword he states that the work represents little else than a consistent systematization of Freud's metapsychologic views. To expound these intricate and often nebulous theories lucidly and consecutively is an undertaking sufficiently great to challenge the mettle of the boldest psychoanalyst. Alexander not only has accomplished this difficult task, but has brought metapsychologic theory into close and plausible relation with clinical experience.

The work, however, is more than a compendium of Freud's theory with the addition of clinical examples. It expands and amplifies what the author describes as the general significance of the neurotic self-punishing mechanism. Of course the sense of guilt has always been adjudged an important rôle in the psychoanalytic interpretation of the genesis of neuroses. One of Freud's earliest discoveries was that the conversion symptoms of hysteria simultaneously satisfied a desire and acted as a punishment. Alexander's present contention is that in compulsion neuroses as well as in hysteria the mechanism of self-punishment is a vital factor, for in the former it "leads to a disappearance or mitigation of conscience anxiety." Only when such anxiety has been alleviated may "wishes repressed because of conscience be gratified in the form of symptoms." Indeed the need for suffering is a constantly repeated theme in Alexander's concept of the origin and continuance of neuroses. He believes that in psychic illness the essential incipient disease process is the turning back of the death impulse with a punitive aim on the Ego. Up to the time of pathologic manifestation the death impulse had been directed against objects outside the personality.

To strengthen this theory he assumes and emphasizes the existence of an unconscious thwarting faculty (a part of the Super-Ego system) which condemns many unconscious strivings just as our conscious critique acts as a censor over some of our conscious activities. Thus the gratification of a condemned tendency by means of a neurotic symptom becomes possible only because the symptom simultaneously constitutes suffering, and through suffering lessens the inhibiting feeling of guilt. When the Ego has been severely or sufficiently punished by the Super-Ego, which at times seems to act with a relentless harshness, it may feel inclined to make a temporary truce with the Id, which it is usually attempting to keep properly subdued. Just as a little boy who has received a whipping from a meticulous mother for playing with naughty street companions, having received punishment for his act, may feel that he has paid the penalty and therefore is

free to permit them to play their rough games with him again, so the Ego, having been chastised by the Super-Ego, is apparently ready to regard leniently the disdained tendencies of the Id. An inherent weakness of the Ego in its inability to cope with the Super-Ego and the Id facilitates the development of neurotic vacillations, contradictions and other symptoms. Another circumstance to which Alexander continually calls attention is the faculty of the Super-Ego not to be deceived by any disguises which may be elaborated by the Ego to convey unconscious yearnings to conscious expression. Among many other ingenious observations is Alexander's distinction between phobias of children and of adults. He believes that the child through projection externalizes a danger arising from within (a part of the Super-Ego's internal perceptive function), whereas in the adult the fear continues to emanate intrapsychically.

The unlabored fluency of the translation of Dr. Lewin and Dr. Glück bespeaks the care and skill that they have bestowed on their task. Their intimate knowledge of psychoanalysis guarantees a discriminating accuracy in the handling of psychoanalytic terminology. Yet with all the success which has attended Alexander's brilliant summary of psychoanalytic metapsychology and the scholarly translation of his American colleagues, the very nature of most of the theoretical material presented makes the book valuable, I might say intelligible, only to those who have a considerable familiarity with psychoanalytic thought.

DIE ROENTGENBEHANDLUNG DER NERVENKRANKHEITEN. By PROFESSOR DR. OTTO MARBURG and DOZ. DR. MAX SGALITZER. Price, 15 marks. Pp. 213. Berlin: Urban & Schwarzenberg, 1930.

A close study of this volume has induced the reviewer to call the attention of American neurologists to a timely and excellent treatise on roentgen treatment for diseases of the nervous system. It is the combined work of Professor Marburg, an ardent therapeutist and skilful clinician, and of Dr. Sgalitzer, the director of the roentgen laboratory connected with Eiselberg's clinic in Vienna. The volume is one of the "Sonderbaende zur Strahlentherapie." The authors have divided the work in such a way that Sgalitzer is responsible for the purely technical and masterly chapters on the physical basis of roentgen rays, on present-day roentgen apparatus and on the effects of the rays on different organs of the body and more especially on malignant tumors and surrounding tissues. Section IV on "Deep Roentgen Therapy," with its discussion of the very complex matter of dosage, will give the neurologist much useful information that is difficult to secure elsewhere. Wherever clinical questions are touched on, as in the roentgen irradiation of the hypophysis, Marburg's hand is clearly visible, and he is responsible for all the sections on the effect of roentgen therapy in various diseases of the nervous system.

The book is a model of its kind. Both authors have made a most exhaustive study of the already vast literature, skilfully arranged in connection with each subdivision. They present a critical analysis of the chief contributions and in every section refer to their own large personal experience. Each section contains a carefully prepared summary of present experience, and while the authors are enthusiastic supporters of roentgen therapy under definite conditions, they remain sober and critical in their estimate of what can be claimed for it in the treatment for nervous diseases and what may be expected of it in the future.

The discriminating judgment of the authors is exemplified best by the summary (p. 84 et seq.) in the section on tumors of the brain: "If we attempt to collate all that has been achieved in cases of definitely verified brain tumors, and adding thereto our own personal experience, we must acknowledge that the actual cure (by roentgen therapy) of an undoubted brain tumor, which has not been operated on, cannot be claimed; but we must concede that tumors can be influenced (by roentgen therapy), especially if they have been reduced in size by operative procedure. This is true, to a degree, of all tumors, including gliomas, although, especially with reference to the latter, an absolute cure is out of the question, and all one can expect is prolongation of life and an improvement of the symptoms.

. . . In a majority of the cases, we are able to influence the general symptoms, and this will mean much, especially with reference to the optic nerve.

"In every definitely diagnosed case of brain tumor that appears to be operable we shall propose surgical removal as the method of choice . . . but in all cases that have been incompletely removed, as in cases of glioma and neurinoma, we shall recommend postoperative roentgen treatment. . . . Postoperative roentgen treatment is also advisable in all cases of radical removal."

The authors are careful to review the methods and dosage employed by others of all nationalities and to caution against possible errors of administration, and thus will prove safe guides in a method of treatment that is still terra incognita to so many. Marburg's personal experience in the treatment for hypophyseal tumors lends especial value to that section in which he declares his belief that these tumors especially can be influenced by adequate roentgen therapy.

Other sections of the treatise have been written with equal care. The chapters on tumors of the spinal cord and of the vertebrae; on meningitis serosa, epilepsy, headaches, neuralgia, dysglandular diseases and multiple sclerosis contain useful summaries of modern claims — always presented with a rare discrimination and absolute fairness. In the section on epilepsy one finds the authors favoring several series of treatments, to be administered with patient care. "We are of the opinion (p. 135) that the claims made for the influence of roentgen therapy on epilepsy will have to be modified so as to imply that in cases which do not improve under drug therapy, roentgen treatment should be attempted . . . that the first series may be unsuccessful; but often after a series of roentgen ray treatments we have achieved satisfactory results." They claim especially good results in traumatic epilepsy and in cases of petit mal, all of which is well worth heeding.

It is hoped, not only that neurologists will make good use of this valuable book of reference, but that some American roentgenologists will give closer attention to the roentgen treatment of nervous diseases. The book merits translation.

BEITRAEGE ZUR MIKROSKOPISCHEN ANATOMIE DES VEGETATIVEN NERVENSYSTEMS. By PHILIPP STOEHR, JR. Price, 10 marks. Pp. 106, with 61 illustrations. Berlin: Urban & Schwarzenberg, 1929.

In this monograph the author has succeeded in giving the reader a concise and excellent survey of present knowledge of the microscopic anatomy of the autonomic nervous system. For want of definite proof of its independence and in the light of his own researches he preferred to call it the vegetative nervous system, a term now often employed collectively for the sympathetic and parasympathetic systems and the vegetative nuclei in the brain stem. In this little volume he recapitulates many of his views and, in brief, all of the known morphologic features which are described at length in his more elaborate work: "Die mikroskopische Anatomie des vegetativen Nervensystems (Berlin, Julius Springer, 1928). Though obviously firmly holding to some of his opinions as to the independence of the so-called vegetative nervous system, to the sanctity of the neuron theory, particularly when applied to sympathetic structures, to the significance of myelination or the lack of myelination of fibers as distinguishing sympathetic fibers from fibers of the cerebrospinal system, etc., he nevertheless was able to impart to this valuable review an impartial and a thoroughly critical character. He draws attention to the inadequacy of histologic methods in attempts to establish the independence of the so-called vegetative system and to isolate with certainty its constituent elements. He cautions against too hastily and poorly substantiated conclusions as to the functions of the various component parts of this system on morphologic grounds alone. He points to the indispensable service of experimental methods as a true guide for anatomic investigations in this field. The recently discovered "rete nervorum," the terminal network about muscle fibers and other cellular structures, serving as a transition between the neuron and the muscle fiber, shows the great difficulty of determining where the nerve fiber ends and the plasma of the innervated structure begins. This he regards as highly significant and is but one of many problems that were at

one time regarded as settled. Then again he raises the questions as how to differentiate a sensory from a motor fiber, a sensory from a motor ganglion cell, a sympathetic from a parasympathetic cell or fiber and points to the inability to identify the axis cylinders of sympathetic ganglion cells and to distinguish them from dendrites. All these problems cannot be solved by known morphologic methods. New steps and, for the most part, an experimental approach will be indispensable to reach a definite decision.

Of the more significant points made in this monograph is the author's belief that in the sympathetic nervous system one deals with a plexiform "closed system" in which the most peripheral parts, in the form of filamentous terminals, are arranged in a plexus about the innervated elements. From the latter they are inseparable, and hence form with them a morphologic and physiologic unit. The monograph is clearly written and well illustrated. Unfortunately the bibliography is incomplete, but this is easily remedied when the larger work by the author is consulted. The monograph will be a valuable addition to the working library of the neuro-anatomist and neurophysiologist.

INVERSIONS-ATMUNG UND GEISTESKRANKHEIT. UNTERSUCHUNGEN ÜBER DIE DYNAMIK DER ATMUNG BEI DER SCHIZOPHRENIE UND VERSUCH EINER PHYSIO-PATHOLOGISCHEN GRUNDLEGUNG DERSELBEN. ZUGLEICH EIN BEITRAG FÜR PROBLEME DER ATMUNGSPATHOLOGIE UND RHINOLOGIE. By DR. MED. OTTO BUSINGER. Price, 3.80 marks. Pp. 48. Munich: Ernst Reinhardt, 1930.

That breathing is a vital issue for the mental integrative functioning must have been felt in the days when primitive humanity shaped its linguistic designations for mind. Breath is the most obvious sign of life and its absence the most obvious sign of death, and this sine qua non gave us the terms psyche, anima, and the Semitic root ruach — breathing or breath being made to stand for the very soul. But the rôle of good or poor breathing in the sense of well-being and the effect of the emotional states on the breathing might well have attracted more attention.

Businger devotes his rhinologic experience and technic directly to a study, explanation and treatment of schizophrenia. After an instructive review of the determiners and the effects of the "inversions" of the normal "parallel stream" of the air column, he gives his observations on schizophrenic patients. He brings the frequency of the status inversus and the evidences of reduction of the gas exchanges (especially studied by S. Fischer) into close relation and attempts a physiopathologic interpretation of schizophrenia. He discusses the importance of the respiratory factor in the sex anomalies, the disorders of affectivity, the energy and volition disorders, the speech, morbid body sensations, hallucinations, the catatonic symptoms, the mimic tonus alterations and even the hyperkinesis and many indirect symptoms. With transformation of the "inversion" into a "parallel stream" in the nasal breathing, he has seen definite readjustments in schizophrenic patients, and he discusses in an interesting manner the importance of a good knowledge of the physics of the air column and the reciprocal relations between the health of the mucous membrane and a proper distribution of the air currents. Among twenty-five cases he obtained a number of far-reaching remissions. It is obviously not a field to be trifled with, and the paper should be studied for all its technical detail before experimentation is started. One cannot help seeing in the report the possibility of another lift in meeting the many difficulties of the often dysplastic psychotic patients. Apart from the possible practical advantages, Businger's study may become a valuable stimulus in the direction of more serious study of the respiratory functions in the total reactions of man.

DIE LEHRE VON DEN NEURONEN UND VOM NEURENCYTIUM UND IHR HEUTIGER STAND. By HANS HELD. Price, 5 marks. Pp. 44, with 21 illustrations. Berlin: Urban & Schwarzenberg, 1929.

The neuron theory, which from the day of its formulation and popularization by Waldeyer and his followers served as an excellent working hypothesis, is again attacked in this monograph by its foremost opponent, Professor His. His objections to the conception of the neuron as an independent and self-sustaining unit are recapitulated and are fortified by new observations, particularly in the field of morphology of the terminal structures or end-organs in the nervous system. The "rete nervorum" of Boeke, identified by many other workers as demonstrating the inability at the present time to separate nerve endings from the innervated structures, is utilized by him as an argument against the neuron theory. The recent opinion expressed by Stoehr that the sympathetic nervous system is constructed as a closed plexiform system in which the apparently free, small, filamentous terminals fuse imperceptibly with the innervated structures is considered by him as a very strong point in favor of his conception of the central nervous system as a "neurencytium." In a few pages the author was able to array all the important observations in support of this conception as well as those which undermine the neuron theory. The position held by the author in the field of anatomy of the central nervous system forbids a lengthy, verbose review of this work. Besides, those who keep an open door for the opposing camps in the neuron theory will be eager to get first hand views held by the master, while those who have decided opinions on the subject will profit by reading this monograph in the original.

FACTORS IN THE SEX LIFE OF TWENTY-TWO HUNDRED WOMEN. By KATHERINE BEMENT DAVIS. Price, $3.50. Pp. 430. New York: Harper & Brothers, 1929.

This volume contains an analysis of the replies made by 1,000 married and 1,200 unmarried women to an extensive questionnaire regarding their sex life. The women were largely of the better educated (college graduate) class. They were "normal" as far as could be ascertained.

For the married groups, the replies regarding the use of contraceptives and the frequency of intercourse and the way in which general and sex factors seemed to influence the happiness of married life were analyzed. Both groups were studied as to the incidence of auto-erotic practices, the periodicity of sex desire and homosexuality. Although there are objections to the validity of data obtained by the questionnaire method, and although the group cannot be considered a "normal one," nearly 30 per cent of 1,000 gave histories of a "nervous breakdown." This is almost the first attempt to collect data on sex life from a large number of women. The author points out that no conclusions as to woman's sex life can be drawn from the material, but the results raise a number of important questions, each of which could be the starting point for more intensive and accurate research. For this reason the book is recommended to all interested in the behavior of human beings.

PSYCHOPHYSIOLOGIE ET PSYCHOPATHOLOGIE DU CORPS THYROIDE. By A. SICCO. Price, 10 francs. Pp. 107. Paris: Félix Alcan, 1927.

This work is an uncritical effort at synthesis of the unsynthesizable, psychology and endocrinology, backed up by references to the works of Bernard, Cannon, Pende, Voronoff and others. Three case reports are given, one of infantile myxedema and two of psychoses with hyperthyroidism, the conclusion being that there is no special form that such psychoses will take. That emotions are not due to the bodily repercussions through the sympathetic system is shown by the presence, after the injection of epinephrine in these cases, of tachycardia, blanching, hypertension and other physical signs of strong emotion without the

least subjective experience of such on the part of the patient. The seventy pages of theory are no better and no worse than other contributions on the same subject. They might well have been left out.

THE MORPHINE HABIT AND ITS PAINLESS TREATMENT. By G. LAUGHTON SCOTT, M.R.C.S., B.A. (OXON.). Price, $2.25. New York: William Wood & Company, 1930.

This small book of less than 100 pages discusses the treatment for the morphine habit. The author believes that the failure in the cure of this condition consists in the fact that not sufficient attention has been paid to the psychic rehabilitation of the addict, and that in most treatments which are being used today the withdrawal of the drug is too rapid, causing an emotional shock in the patient from which he does not recover, or at least it creates in him a lack of desire for future withdrawal treatments. The author advocates a more gradual withdrawal, for in this way he has obtained good results. There is nothing particularly new in the experience of the author, and the book does not furnish anything new.

ENDOCRINE DISORDERS. By PROF. HANS CURSCHMANN. Price, $4. Pp. 181. New York: Oxford University Press, 1929.

So far as the reviewer knows this is the best small book on endocrine disorders in the English language. It takes up in order the diseases of the thyroid, parathyroid, pituitary, the suprarenals, gonads, pineal gland, status thymolymphaticus and pluriglandular insufficiency. The subject is well presented in an orderly manner. The clinical picture is adequate, and suggestions are made for treatment. Not too many claims are made for the effects of hormone therapy. It is altogether a safe and sane book and is welcome.

HIRNPATHOLOGISCHE BEITRÄGE. By DR. KARL SCHAFFER, Budapest. Volumes 8 and 9. Pp. 294 and 423. Budapest: Karl Schaffer, 1929 and 1930.

The eighth and ninth volumes of reprints which are issued under the auspices of Prof. Karl Schaffer's Neuropsychiatric Department of the University of Budapest confer, like their predecessors, great honor to this distinguished Hungarian neurologist and his co-workers. The ninth volume is particularly interesting, as it is dedicated to Professor Emeritus Solomon Eberhard Henschen of Stockholm on his Golden Doctor's Jubilee.

NEUROANATOMY (A LABORATORY GUIDE). By J. H. GLOBUS. Fifth edition, revised and enlarged. Price, $3.50. Pp. 93. New York: Paul B. Hoeber, Inc., 1930.

The fact that five editions of this work have appeared during a period of five years testifies to the excellency of the conception and the efficiency with which the book has been written. It is recommended to all students of neuroanatomy.

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